AF/1615/4

TRANSMITTAL OF APPEAL BRIEF (Large Entity)

Docket No. 112703-035

In Re Application Of: **Ream et al.**

Serial No.	Filing Date	Examiner	Group Art Unit
09/286,818	April 6, 1999	T. Page	1615

Invention: **PHARMACEUTICAL CHEWING GUM FORMULATIONS**

TO THE COMMISSIONER FOR PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed on **July 28, 2003**

The fee for filing this Appeal Brief is: **$320.00**

☒ A check in the amount of the fee is enclosed.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

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Signature

Dated: **September 29, 2003**

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Adams 10/1/03 #1 of 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants:	Ream et al.
Appl. No.:	09/268,818
Conf. No.:	5472
Filed:	April 6, 1999
Title:	PHARMACEUTICAL CHEWING GUM FORMULATIONS
Art Unit:	1615
Examiner:	T. Page
Docket No.:	112703-035

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' APPEAL BRIEF

Dear Sir:

Appellants submit this Appeal Brief in support of the Notice of Appeal filed on July 28, 2003. This Appeal is taken from the Final Rejection dated April 7, 2003.

I. REAL PARTY IN INTEREST

The real party in interest for the above-identified patent application on Appeal is Wm. Wrigley Jr. Company by virtue of an Assignment dated June 14, 1999 and June 18, 1999 and recorded at REEL/FRAME: 010060/0375 in the United States Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES

Appellants do not believe there are any known appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision with respect to the above-identified Appeal.

III. STATUS OF THE CLAIMS

Claims 1-12 and 19-22 are pending in this application. A copy of appealed claims 1-12 and 19-22 is attached in the appendix. In the Final Office Action dated April 7, 2003, claims 1-6 and 19-22 stand rejected under 35 U.S.C. § 112; claims 1-4, 6-11, 19, 20 and 22 stand rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,013,716 ("*Cherukuri*"); claims 5, 2, and 21 stand rejected in view of Cherukuri; and claims 1, 7 and 19 stand rejected in view of *Cherukuri* and U.S. Patent No. 5,922,347 ("*Hausler*"). A copy of the Final Office Action is appended hereto as Exhibit A of the Supplemental Appendix and a copy of each of the cited references is appended hereto as Exhibits B and C of the Supplemental Appendix.

IV. STATUS OF THE AMENDMENTS

No Amendments After Final were filed.

V. SUMMARY OF THE INVENTION

The present invention generally relates to the delivery of medicaments and other agents. More specifically, the present invention relates to the delivery of medicaments and agents using chewing gum formulations. (Specification, page 1, lines 6-8.)

It is of course known to provide agents to individuals for various purposes. These agents can be used to treat diseases and as such are typically referred to as drugs or medicaments. Likewise, drugs or medicaments can be used for prophylactic purposes. Still, it is known to provide agents to an individual for a variety of non-medical purposes including enhancing performance or maintaining or initiating alertness. There are a great variety of such agents. These agents run the gamut from stimulants such as caffeine to drugs such as analgesics, tranquilizers, cardiovascular products, insulin, etc. Some such agents are taken on an as needed basis while other agents must be taken at regular intervals by the individual. (Specification, page 1, lines 9-17.)

Typically, drugs (medicaments) are administered parenterally or enterally. Of course, parenteral administration is the administration of a drug intravenously directly into the blood stream. Enteral refers to the administration of a drug into the gastrointestinal tract. In either

case, the goal of the drug administration is to move the drug from the site of administration towards the systemic circulation. (Specification, page 1, lines 18-22.)

Except when provided intravenously, a drug must traverse several semipermeable cell membranes before reaching general circulation. These membranes act as a biological barrier that inhibits the passage of drug molecules. There are believed to be four processes by which drugs move across a biological barrier: passive diffusion; facilitated diffusion; active transport; and pinocytosis. (Specification, page 1, lines 23-27.)

In determining the efficacy of a drug and the effectiveness of the use of a drug to treat a disease, drug absorption is a critical concern. Drug absorption refers to the process of drug movement from the site of administration toward the systemic circulation. (Specification, page 2, lines 7-10.)

Oral administration of drugs is by far the most common method. When administered orally, drug absorption usually occurs due to the transport of cells across the membranes of the epithelial cells within the gastrointestinal tract. Absorption after oral administration is confounded by numerous factors. These factors include differences down the alimentary cannel in: the luminal pH; surface area per luminal volume; perfusion of tissue, bile, and mucus flow; and the epithelial membranes. (Specification, page 2, lines 11-7.)

A further issue effecting the absorption of orally administered drugs is the form of the drug. Most orally administered drugs are in the form of tablets or capsules. This is primarily for convenience, economy, stability, and patient acceptance. Accordingly, these capsules or tablets must be disintegrated or dissolved before absorption can occur. There are a variety of factors capable of varying or retarding disintegration of solid dosage forms. Further, there are a variety of factors that effect the dissolution rate and therefore determine the availability of the drug for absorption. (Specification, page 2, lines 18-25.)

Not only is drug absorption an issue in drug delivery, but, also the bioavailability of the drug is also critical. Bioavailability is defined as the rate at which and the extent to which the active moiety (drug or metabolite) enters the general circulation, thereby gaining access to the site of action. Bioavailability depends upon a number of factors, including how a drug product is designed and manufactured, its physicochemical properties, and factors that relate to the physiology and pathology of the patient. (Specification, page 3, lines 4-10.)

Although parental administration does provide a method for eliminating a number of the variables that are present with oral administration, parental administration is not a preferable route. Typically, parental administration requires the use of medical personnel and is just not warranted nor practical for the administration of most agents and drugs, e.g., analgesics. Even when required parenteral administration is not preferred due to patient concerns including comfort, infection, etc., as well as the equipment and costs involved. However, despite best efforts certain therapies require parenterally injected drugs. For example, research for decades has focused on an attempt to deliver insulin to an individual through a non-parental means. Despite such efforts today insulin is still only administered intravenously. (Specification, page 3, line 23 to page 4, line 1.)

When a drug rapidly dissolves from a drug product and readily passes across membranes, absorption from most site administration tends to be complete. This is not always the case for drugs given orally. Before reaching the vena cava, the drug must move down the alimentary cannel and pass through the gut wall and liver, which are common sites of drug metabolism. Thus, the drug may be metabolized before it can be measured in the general circulation. This causes a decrease in drug input that is called the first pass effect. A large number of drugs show low bioavailability owing to an extensive first pass metabolism. The two other most frequent causes of low bioavailability are insufficient time in the GI tract and the present of competing reactions. See *Merck Manual* at page 2602. Bioavailability considerations are most often encountered for orally administered drugs. Differences in bioavailability can have profound clinical significance. (Specification, page 3, lines 11-22.)

The present invention provides improved methods for delivering medicaments and other agents to an individual as well as improved formulations including such medicaments and agents. Pursuant to the present invention, a medicament or agent is contained in a chewing gum formulation. In contrast to prior such formulations, the medicament or agent is contained directly in the chewing gum composition, e.g., not in a coating around the chewing gum. (Specification, page 7, lines 14-19.)

Accordingly, as the chewing gum is chewed, the medicament or agent is released into the saliva. During continual chewing, the medicament or agent in the saliva is then forced due to the pressure created by the chewing through the oral mucosa in the buccal cavity. The oral mucosa

has a thin epithelium and a rich vascularity. Thus, the oral mucosa favors drug absorption. In contrast to a typically orally ingested drug, wherein the solution is in contact too briefly for absorption to be appreciable through the oral mucosa, it is believed that during chewing, the agent and/or medicament remains in the buccal cavity and is forced through the oral mucosa. Also it has been surprisingly found that an increase in the absorption of the drug is achieved as well as an increase in the bioavailability of the drug as compared to typical oral administration. It has been found that the drug or agent is absorbed much quicker than if it was swallowed as in a typical oral administration. Indeed, the absorption approaches that of a parental administration, and bioavailability is also much greater than oral administration. (Specification, page 7, line 20 to page 8, line 1.)

It has also been surprisingly found that less medicament or agent can be placed in the chewing gum than is typically orally administered to an individual to achieve an effect and the same bioequivalence can be achieved. In fact, it has been surprisingly found that in certain instances, for at least certain drugs and agents, the administration of the medicament or agent using chewing gum through the buccal cavity can provide an increase effect even as compared to parenteral administration. (Specification, page 8, lines 2-7.)

For example, caffeine is commonly used as a stimulant to alleviate the effects of sleep deprivation. It is almost completely metabolized in the liver and therefore classified as a low clearance, flow independent drug. This means its rate of inactivation is unaffected by delivery to the liver and can only be modified by a change in the hepatic enzyme activity. (Specification, page 8, lines 8-12.)

The pharmacokinetics of caffeine have been well documented and there is no significant difference between oral and intravenous administration. However, data set forth in detail below, suggests that the absorption rate constant (Ka) is significantly increased when caffeine is administered through chewing gum. This means that the caffeine is moving into the systemic circulation at a significantly faster rate. A similar change in the onset of dynamic response has also been noted, e.g., alertness and performance. (Specification, page 8, lines 13-19.)

It has additionally been surprisingly found that for at least certain agents that placing the agent in the chewing gum can have a triggering effect on the agent that may be in the systemic circulation. For example, it has been found that with respect to caffeine that is ingested orally,

that after the ingestion of a certain amount of caffeine, and the elapse of a certain period of time, that further ingestion of caffeine has a negligible effect on the individual. However, upon chewing gum with caffeine there has been observed a triggering effect that appears to create a synergistic effect with the caffeine that is in the systemic circulation. It is believed that this triggering effect will also be present with other agents, e.g., analgesics. (Specification, page 8, lines 13-19.)

It is envisioned, that a variety of different medicaments and agents can be used in the chewing gum. For example, such agents include, *inter alia*, stimulants such as caffeine. Generally, such medicaments include, inter alia, analgesics, antibiotics, antivirals, antihistamines, anti-inflammatories, decongestants, antacids, muscle relaxants, psychotherapeutic agents, insulin, and cardiovascular agents. It is envisioned, that depending on the medicament, the resultant chewing gum can be used to treat, inter alia: coughs; colds; motion sickness; allergies; fevers; pain; inflammation; sore throats; cold sores; sinus problems; diarrhea; diabetics; depression; anxiety; and other maladies and symptoms. Specific agents/medicaments include, by way of example and not limitation: caffeine; aspirin; acetaminophen; ibuprofen; hydroxycitric acid; chromium picolinate; phosphatidylserine; nicotine; insulin; Echinacea purpurea; zinc; vitamin C; ginseng; kola nut; kaua kaua; and chamomile. (Specification, page 8, line 29 to page 8, line 9.)

Preferably, the agents or medicaments are contained in the chewing gum formulation at levels of approximately 50 micrograms to 500 milligrams. The specific levels will depend on the active ingredient. For example, if chromium picolinate is the active ingredient in an embodiment, it would be present at a level of 50 micrograms per serving (2.8 grams stick of gum); aspirin would be preset at a level of 325 milligrams per 2.8/gram serving (stick). (Specification, page 9, lines 10-15.)

The level of medicament or agent in the chewing gum formulation is selected so as to create, when the gum is chewed, a sufficiently high concentration of the medicament or agent in the saliva. (Specification, page 9, lines 16-19.)

For example, when the agent is a stimulant such as nicotine or caffeine, the level of the stimulant in the chewing gum should be such that it creates a saliva content of stimulant of approximately 15 to 440 ppm when the chewing gum is chewed for 2 minutes. At this level, a

sufficient amount of stimulant will be delivered to the chewer to create the effects set forth in the application. If a medicament is used such as a medicinal (e.g., analgesics), sufficient medicinal should be present in the chewing gum to create a saliva content of approximately 1700 to approximately 4400 ppm after the chewing gum has been chewed for 2 minutes. For a botanicals (e.g., chamomile, kava, kola, nut, ginseng, and Echinacea), the agent should be present in a sufficient amount to create a saliva content of approximately 85 to 1100 ppm when the chewing gum is chewed for 2 minutes. For a metabolizer, for example, chromium picolineate and hydroxi-chitic acid, the agents should be present in an amount to create a saliva content of approximately 0.5 to about 900 ppm when chewed for at least two minutes. If the agent is a vitamin or mineral (e.g., phosphatidy serine, vitamin C, and zinc), the agent should be present in the amount to create a saliva content of the vitamin or mineral of approximately 10 to about 250 ppm when chewed for 2 minutes. (Specification, page 9, line 19 to page 10, line 3.)

Pursuant to the present invention, depending on the agent or medicament, the dosing regiment will change. For example, if the medicament is an analgesic, the chewing gum would be taken on an as needed basis. Of course, similar to the oral administration of an analgesic, there would be restrictions on the number of pieces of chewing gum, chewed, for example, not more often than one stick every four hours and not more often than four to five times a day. (Specification, page 9, lines 4-9.)

If the agent is a stimulant such as caffeine to be used to enhance performance than the chewing gum would be chewed, in a preferred embodiment ten minutes or less before the performance. As set forth below in the experiment, it has been surprisingly found that another 5 minutes of chewing a chewing gum including caffeine a high level of alertness is achieved. (Specification, page 10, lines 10-14.)

The medicament or agent can be contained in a variety of different chewing gum compositions. Referring now to the chewing gum, pursuant to the present invention, the chewing gum including the medicament or agent may be based on a variety of different chewing gums that are known. For example, the chewing gums can be low or high moisture, sugar or sugarless, wax containing or wax free, low calorie (via high base or low calorie bulking agents), and/or may contain dental agents. (Specification, page 10, lines 15-20.)

Chewing gum generally consists of a water insoluble gum base, a water soluble portion, and flavor. The water soluble portion dissipates with a portion of the flavor of the gum over a period of time during chewing. The gum base portion is retained in the mouth throughout the chew. The insoluble gum base generally comprises elastomers, resins, fats and oils, softeners and inorganic fillers. The gum base may or may not include wax. (Specification, page 10, lines 21-26.)

In addition to a water insoluble gum base portion, a typical chewing gum composition includes a water soluble bulk portion and one or more flavoring agents. The water soluble portion can include bulk sweeteners, high intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, acidulants, fillers, antioxidants, and other components that provide desired attributes.

If the medicament or agent is water soluble in the chewing gum, it preferably will include a base/emulsifier system which leads to the desired concentration of the medicament in the saliva (more hydrophilic balance). If the medicament or agent is water insoluble, the chewing gum preferably includes a base/emulsifier system which leads to the desired concentration of the medicament in the saliva (more lipophilic balance). (Specification, page 13, line 30 to page 14, line 4.)

In manufacturing the chewing gum including the agent or ingredient, the agent or medicament is added, preferably, early on in the mix. The smaller the amount of active ingredient used, the more necessary it becomes to preblend that particular ingredient to assume uniform distribution throughout the batch of gum. Whether a preblend is used or not, in a preferred embodiment, the agent or medicament should be added within the first five minutes of mixing. (Specification, page 14, lines 5-10.)

By way of example, and not limitation, examples of some chewing gum formulations including a medicament or agent are provided on pages 14 and 15 of the specification. Appellants have also conducted a number of experiments that demonstrate the beneficial effects of Appellants' invention. (Specification, pages 16-26.)

VI. ISSUES

The issue on Appeal is as follows:

1. Is the claim term "typical amount" definite as defined by claims 1-6 and 19-22?
2. Would the methods of delivering a medicament and method of reducing the amount of agent as defined in claims 1-4, 6-11, 19, 20 and 22 have been non-obvious over *Cherukuri*?
3. Would the methods of delivery a medicament and methods of reducing the amount of agent as defined in claims 5, 12 and 21 have been non-obvious over *Cherukuri*?
4. Would the methods of delivering a medicament and methods of reducing the amount of agent as defined in claims 1, 7 and 19 have been non-obvious over *Cherukuri* and *Hausler*?

VII. GROUPING OF THE CLAIMS

Appellants argue for the separate patentability of each of the independent claims separate and apart from each other set forth in detail below pursuant to the requirements of 37 C.F.R. § 1.192(7), unless otherwise specified.

VIII. ARGUMENT

A. The Claimed Invention -- Independent Claims

On appeal, claims 1, 7 and 19 are the sole independent claims. Independent claims 1, 7 and 19 are provided below as follows:

Independent Claim 1 recites a method for delivering a medicament to an individual. The method includes the steps of providing a chewing gum consisting of ingredients selected from the group consisting of elastomers, resins, fats, oils, softeners, fillers, waxes, colorants, antioxidants, plasticizers, texturizers, emulsifiers, whiteners, acidulants, bulking agents, essential oils, sweeteners, and flavors, and at least one medicament, wherein the ingredients and medicament have a uniform distribution throughout the chewing gum including less than the typical amount of medicament that is swallowed by the individual to achieve an effect; chewing the chewing gum to cause the medicament to be released from the chewing gum composition

into the buccal cavity of the individual; and continuing to chew the chewing gum thereby creating a fluid pressure causing the medicament to enter the systemic system of the individual through an oral mucosa of the individual.

Independent Claim 7 recites a method for reducing the amount of agent necessary to achieve an effect in an individual as compared a typical agent that is swallowed. The method includes the steps of providing a chewing gum consisting of ingredients selected from the group consisting of elastomers, resins, fats, oils, softeners, fillers, waxes, colorants, antioxidants, plasticizers, texturizers, emulsifiers, whiteners, acidulants, bulking agents, essential oils, sweeteners, flavors, and at least one agent that is typically swallowed by an individual to achieve a specific effect, wherein the ingredients and agent are uniformly distributed throughout the chewing gum, the chewing gum including less than the typical amount of agent that is swallowed by the individual to achieve the effect; chewing the chewing gum and thereby causing the agent to be released into the salvia of the individual; and continuing to chew the chewing gum forcing the agent through an oral mucosa contained in a buccal cavity of the individual.

Independent Claim 19 recites a method of delivering a medicament. The method includes the steps of providing a chewing gum consisting of ingredients selected from the group consisting of elastomers, resins, fats, oils, softeners, fillers, waxes, colorants, antioxidants, plasticizers, texturizers, emulsifiers, whiteners, acidulants, bulking agents, essential oils, sweeteners, flavors, and at least one medicament. The ingredients and medicament are uniformly distributed throughout the chewing gum, wherein the chewing gum including less than the typical amount of medicament that is swallowed by the individual to achieve an effect. The method further includes chewing the chewing gum for at least 2 minutes in a buccal cavity of an individual chewing the chewing gum.

B. The Rejection

Claims 1-6 and 19-22 have been rejected under 35 U.S.C. § 112, ¶2. The Patent Office asserts that the claim term "typical amount" is indefinite in meaning.

Claims 1-12 and 19-22 have been rejected under 35 U.S.C. § 103 as being unpatentable over *Cherukuri*. The Patent Office asserts that *Cherukuri* discloses or suggests each and every feature of the claimed invention.

Claims 1, 7 and 19 have been rejected under 35 U.S.C. § 103 over *Cherukuri* and *Hausler*. The Patent Office asserts that the combination of references discloses or suggests each and every feature of the claimed invention. In this regard the Patent Office principally relies an *Cherukuri* and thus further relies on *Hausler* to remedy the deficiencies of same.

C. Claims 1-6 and 19-22 are Sufficiently Definite to Meet the Requirements Under 35 U.S.C. § 112

Appellants respectfully submit that the rejection of claims 1-6 and 19-22 under 35 U.S.C. § 112, ¶2 should be reversed. Claims 1-6 and 19-22 comply with the requirements of 35 U.S.C. §112, ¶ 2. The claim term "typical amount" is a clearly defined claim term as fully supported in the Specification. In this regard, one of ordinary skill in the art would be apprised as to the meaning of this term in view of the claim language as further supported in the specification. Therefore, Appellants respectfully submit that this rejection is incorrect as a matter of law and fact.

1. The Applicable Law

With respect to 35 U.S.C. § 112, ¶ 2, the standard for determining whether the definitiveness requirement has been met is "whether those skilled in the art would understand what is claimed when the claim is read in light of the Specification." *Orthokinetics Inc. v. Safety Travel Chairs Inc,* 1 U.S.P.Q. 2d 1081-1088 (Fed. Cir. 1986). "If the claims, read in light of the Specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the Courts can demand no more." *North American Vaccine Inc. v American Cyanamid Co.,* 28 U.S.P.Q. 2d 1333, 1339 (Fed. Cir. 1993). In this regard, "[p]atent law allows the inventor to be his own lexicographer ... [T]he specification aids in ascertaining the scope and meaning of the language employed in the claims inasmuch as words must be used in the same way in both the claims and the specification. *United States v. Teletronics, Inc.,* 8 U.S.P.Q. 2d 1217, 1220 (Fed. Cir. 1988).

"By statute, 35 U.S.C. 112, Congress has placed no limitations on how an applicant claims his invention, so long as the specification concludes with claims which particularly point out and distinctly claim that invention." *In re Pilkington,* 162 U.S.P.Q. 145, 148 (C.C.P.A. 1996).

2. The Rejection of Claims 1-6 and 19-22 under 35 U.S.C. § 112 Should be Reversed Because the Claim Term "typical amount" is Sufficiently Clear

Appellants respectfully submit that the rejection of claims 1-6 and 19-22 under 35 U.S. C. § 112, ¶ 2 is improper as a matter of law or fact, and therefore, should be reversed. The claim term "typical amount" is sufficiently clear in scope and meaning and thus fully complies with 35 U.S.C. § 112.

Of the claims at issue, claims 1 and 19 are the sole independent claims and thus the remaining claims at issue depend from either claim 1 or claim 19. Independent claims 1 and 19 each relate to methods for delivering a medicament to an individual. Each claim recites, in part, providing a chewing gum that includes gum ingredients wherein the chewing gum includes less than the typical amount of medicament that is swallowed by the individual to achieve an effect as supported in the specification.

For example, the specification provides that less medicament or agent can be placed in the chewing gum than is typically orally administered (e.g., swallowed) to an individual to achieve an effect. See, specification, page 8, lines 3-7. Further, the specification provides that most orally administered drugs (e.g., medicaments) are in the form of tablets or capsules. See, specification, page 2, lines 19. Indeed, Appellants conducted an experiment to compare the caffeine delivery effects between chewing gum pieces with 50 mg of caffeine made pursuant to an embodiment of the present invention and chewable No-Doz® tablets with 100 mg of caffeine. See, specification, Experiment No. 2, beginning on page 16. In view of same, one skilled in the art would recognize that the chewing gum as claimed includes an amount of medicament, such as caffeine, that is less than an amount of the same medicament as swallowed, such as via oral administration in the form of a tablet or capsule. Therefore, Appellants believe that the claimed invention as defined in claims 1-6 and 19-22 is definite in scope and meaning and thus complies with 35 U.S.C. §112, ¶2.

Accordingly, Appellants respectfully request that the rejection of claims 1-16 and 19-22 under 35 U.S.C. §112, ¶2 be reversed.

D. The Patent Office Has Failed to Establish a *Prima Facie* Case of Obviousness

Appellants respectfully submit that the rejection of claims 1-12 and 19-22 under 35 U.S.C. § 103(a) should be reversed based on the fact that the Patent Office has failed to establish a *prima facie* case of obviousness. Appellants submit that the cited references, even if combinable, fail to disclose or suggest a number of features of the claimed invention. Further, Appellants believe that the Patent Office has relied on hindsight reasoning in support of the combination and/or modification of the cited art to allegedly arrive at the claimed invention.

1. The Applicable Law

The Federal Circuit has held that the legal determination of an obviousness rejection under 35 U.S.C. § 103 is:

> whether the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made...The foundational facts for the prima facie case of obviousness are: (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; and (3) the level of ordinary skill in the art...Moreover, objective indicia such as commercial success and long felt need are relevant to the determination of obviousness...Thus, each obviousness determination rests on its own facts.

In re Mayne, 41 U.S.P.Q.2d 1451, 1453 (Fed. Cir. 1997).

In making this determination, the Patent Office has the initial burden of proving a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). This burden may only be overcome "by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings." *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). "If the examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Further, the Federal Circuit has held that it is "impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the

claimed invention is rendered obvious." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention" *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988).

Moreover, the Federal Circuit has held that "obvious to try" is not the proper standard under 35 U.S.C. §103. *Ex parte Goldgaber*, 41 U.S.P.Q.2d 1172, 1177 (Fed. Cir. 1996). "An-obvious-to-try situation exists when a general disclosure may pique the scientist curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claim result would be obtained if certain directions were pursued." *In re Eli Lilly and Co.*, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).

2. The § 103 Rejection of claims 1-12 and 19-22 Should Be Reversed Because the Patent Office Has Failed to Establish a *Prima Facie* Case of Obviousness

Appellants respectfully submit that the Patent Office has failed to establish a *prima facie* case of obviousness with respect to the rejection of claims 1-12 and 19-22 under 35 U.S.C. § 103. At the outset, Appellants submit that the references, even if combinable, fail to disclose or suggest, at a minimum, the medicament delivery features as claimed. Therefore, Appellants submit that the references, alone or even if combinable, fail to disclose or suggest the claimed invention as required by claims 1-12 and 19-22.

a. The Medicament Delivery Features of the Claimed Invention

Of the pending claims at issue, claims 1, 7 and 19 are the sole independent claims. Claims 1 and 19 relate to methods for delivering a medicament to an individual as discussed above. Claims 1 and 19 each recite, in part, providing a chewing gum that includes ingredients and at least one medicament wherein the medicament and the ingredients are uniformly distributed throughout and wherein the chewing gum includes less than a typical amount of medicament that is swallowed by the individual to achieve an effect. Claim 1 further recites chewing the chewing gum to cause the medicament to be released from the chewing gum into the buccal cavity of the individual; and continuing to chew the chewing gum thereby creating a fluid pressure, thus causing the medicament to enter the systemic system of the individual through an

oral mucosa of the individual. Claim 19 further recites that the chewing gum is chewed for at least 2 minutes in a buccal cavity of the individual.

Claim 7 relates to a method for reducing the amount of agent necessary to achieve an effect on an individual as compared to a typical agent that is swallowed. The method includes providing a chewing gum with less than the typical amount of agent that is swallowed by the individual to achieve the effect; chewing the chewing gum; and continuing to chew the chewing gum, thus forcing the agent through an oral mucosa contained in a buccal cavity of the individual.

According to the present invention, the medicament or agent is released into the saliva. During continual chewing, the medicament or agent in the saliva is then forced due to the pressure created by the chewing through the oral mucosa in the buccal cavity. The oral mucosa has a thin epithelium and a rich vascularity. Thus, the oral mucosa favors drug absorption.

Further, it has been surprisingly found that an increase in the absorption of the drug is achieved as well as an increase in the bioavailability of the drug as compared to typical oral administration. In this regard, the drug or agent is absorbed much quicker than if it was swallowed as in a typical oral administration. Indeed, the absorption approaches that of a parental administration, and bioavailability is also much greater than oral administration.

Moreover, it has also been surprisingly found that less medicament or agent can be placed in the chewing gum than is typically orally administered to an individual to achieve an effect and the same bioequivalence can be achieved. In fact, it has been surprisingly found that in certain instances, for at least certain drugs and agents, the administration of the medicament or agent using chewing gum through the buccal cavity can provide an increase effect even as compared to parenteral administration.

b. The Cited References Fail to Disclose or Suggest the Medicament Delivery Formulation Features of the Claimed Invention

Appellants believe that the cited art, even if combinable, fails to disclose or suggest at least a number of features of the claimed invention. For example, the *Cherukuri* reference is deficient with respect to the medicament delivery features as claimed. At the outset, the Patent Office even admits that *Cherukuri* fails to teach chewing and continuing to chew the chewing

gum, thus causing the medicament to absorb through the oral cavity as claimed, let alone that the chewing gum is chewed for at least 2 minutes and/or that the chewing gum creates a saliva content of medicament of approximately 1700 ppm to about 4400 ppm.

Indeed, the clear emphasis of *Cherukuri* relates to masking unpleasant taste in ingestible products and not drug delivery, let alone drug delivery from chewing gums. See, *Cherukuri*, col. 3, lines 38-48. For example, *Cherukuri* provides that a taste masking agent can be applied to a laundry list of medicament drugs (See, column 6) or separately to a laundry list of different types of gums (See, columns 8-10). But, nowhere does *Cherukuri* disclose or suggest a chewing gum with a medicament that can be chewed and continued to chew to provide an effective delivery of the medicament to an individual chewing same as required by the claimed invention.

Moreover, *Cherukuri* effectively teaches away from chewing and continuing to chew a chewing gum that includes a medicament less than a typical amount of the same medicament as swallowed, such as in tablet or capsule form, as required by the claimed invention. *Cherukuri* merely provides that the medicament can be administered in physical forms, such as free forms, encapsulated forms or mixtures thereof, in ordinary dosage amounts. See, *Cherukuri*, col. 7, lines 3-17. As previously discussed, Appellants have found that less medicament or agent can be placed in the chewing gum than is typically orally administered to an individual to achieve an effect and the same bioequivalence can be achieved. In fact, Appellants have found that in certain instances, for at least certain drugs and agents, the administration of the medicament or agent using chewing gum through the buccal cavity can provide an increased effect even as compared to parenteral administration as previously discussed. Based on at least these reasons, one skilled in the art would recognize that *Cherukuri*, on its own, is deficient with respect to the claimed invention.

Further, Appellants do not believe that *Hausler*, even if combinable, can remedy the deficiencies of *Cherukuri*. The Patent Office merely relies on *Hausler* for its alleged teachings regarding a stable chewing gum formulation that includes an active drug. Contrary to the Patent Office's position, this is not sufficient in scope to overcome *Cherukuri*'s deficiencies directed to the medicament delivery features as claimed, such as chewing and continuing to chew a chewing gum that includes a medicament to facilitate medicament delivery to an individual chewing same wherein the chewing gum includes less than a typical amount of the medicament as swallowed.

What the Patent Office has done is to rely on hindsight reasoning in support of the obviousness rejection in view of *Hausler* and *Cherukuri*. Indeed, *Cherukuri* effectively teaches away form the claimed invention as previously discussed. Thus, Appellants do not believe that one skilled in the art would be inclined to modify *Cherukuri* in view of *Hausler* to arrive at the claimed invention.

Based on at least these reasons, Appellants believe that the cited art is deficient with respect to the claimed invention. Therefore, Appellants respectfully submit that the cited art, alone or even if combinable, fails to render obvious the claimed invention.

Accordingly, Appellants respectfully request that the rejection of claims 1-12 and 19-22 under 35 U.S.C. § 103 be reversed.

IX. CONCLUSION

Appellants' claimed invention set forth in claims 1-12 and 19-22 is neither taught nor suggested by the cited references, either alone or in combination. The Patent Office has failed to establish a *prima facie* case of obviousness with respect to the rejection of claims 1-12 and 19-22. Accordingly, Appellants respectfully submit that the rejection of pending claims 1-12 and 19-22 as being obvious is erroneous in law and in fact and should therefore be reversed by this Board. Moreover, Appellants respectfully submit that the rejection of claims 1-6 and 19-22 under 35 U.S.C. § 112 is erroneous in law and fact and should also be reversed.

Respectfully submitted,

BELL, BOYD & LLOYD LLC

BY _____

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Date: September 29, 2003

APPENDIX

1. A method for delivering a medicament to an individual comprising the steps of: providing a chewing gum consisting of ingredients selected from the group consisting of elastomers, resins, fats, oils, softeners, fillers, waxes, colorants, antioxidants, plasticizers, texturizers, emulsifiers, whiteners, acidulants, bulking agents, essential oils, sweeteners, and flavors, and at least one medicament, the ingredients and medicament having a uniform distribution throughout the chewing gum including less than the typical amount of medicament that is swallowed by the individual to achieve an effect;

chewing the chewing gum to cause the medicament to be released from the chewing gum composition into the buccal cavity of the individual; and

continuing to chew the chewing gum thereby creating a fluid pressure causing the medicament to enter the systemic system of the individual through an oral mucosa of the individual.

2. The method of Claim 1 wherein the chewing gum is chewed for at least 2 minutes.

3. The method of Claim 1 wherein the chewing gum creates a saliva content of medicament of approximately 1700 to about 4400 ppm.

4. The method of Claim 1 wherein the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; insulin; vitamins; minerals; and cardiovascular agents.

5. The method of Claim 1 including the steps of chewing a chewing gum including the medicament at least twice a day.

6. The method of Claim 1 wherein the chewing gum creates a saliva content of medicament of approximately 4 ppm to about 450 ppm.

7. A method for reducing the amount of agent necessary to achieve an effect in an individual as compared a typical agent that is swallowed comprising the steps of: providing a chewing gum consisting of ingredients selected from the group consisting of elastomers, resins, fats, oils, softeners, fillers, waxes, colorants, antioxidants, plasticizers, texturizers, emulsifiers, whiteners, acidulants, bulking agents, essential oils, sweeteners, flavors, and at least one agent that is typically swallowed by an individual to achieve a specific effect, the ingredients and agent being uniformly distributed throughout the chewing gum, the chewing gum including less than the typical amount of agent that is swallowed by the individual to achieve the effect;

chewing the chewing gum and thereby causing the agent to be released into the salvia of the individual; and

continuing to chew the chewing gum forcing the agent through an oral mucosa contained in a buccal cavity of the individual.

8. The method of Claim 7 wherein the agent is a medicament.

9. The method of Claim 8 wherein the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; and cardiovascular agents.

10. The method of Claim 7 wherein the chewing gum is chewed for at least 2 minutes.

11. The method of Claim 7 wherein the chewing gum creates a saliva content of medicament of approximately 15 to about 440 ppm.

12. The method of Claim 7 including the steps of chewing a chewing gum including the medicament at least twice a day.

19. A method of delivering a medicament comprising the steps of providing a chewing gum consisting of ingredients selected from the group consisting of: elastomers, resins,

fats, oils, softeners, fillers, waxes, colorants, antioxidants, plasticizers, texturizers, emulsifiers, whiteners, acidulants, bulking agents, essential oils, sweeteners, flavors, and at least one medicament, the ingredients and medicament being uniformly distributed throughout the chewing gum, the chewing gum including less than the typical amount of medicament that is swallowed by the individual to achieve an effect; and

chewing the chewing gum for at least 2 minutes in a buccal cavity of an individual chewing the chewing gum.

20. The method of Claim 19 wherein the medicament is chosen from the group consisting of: analgesics; muscle relaxants; antibiotics; antivirals; antihistamines; decongestants; anti-inflammatories; antacids; psychotherapeutic agents; and cardiovascular agents.

21. The method of Claim 19 including the steps of chewing a chewing gum including the medicament at least twice a day.

22. The method of Claim 19 wherein two pieces of chewing gum are chewed at a time.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/286,818	04/06/1999	RONALD L. REAM	P99.0082	5472

29156 7590 04/07/2003

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EXAMINER
TRAN, SUSAN T

ART UNIT	PAPER NUMBER
1615	36

DATE MAILED: 04/07/2003

DUE: 7-7-03

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/286,818	REAM ET AL.	
	Examiner	Art Unit	
	Susan Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of applicant's Amendment filed 01/30/03.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 19 are indefinite in the use of the phrase "typical amount". What is typical amount? The examiner has not been able to determine what can be considered a typical amount? Thus, the metes and bounds of the patent protection desired are unascertainable. Further clarification is suggested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-11, and 19, 20, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherukuri et al. US 5,013,716.

Cherukuri teaches chewing gum composition comprising elastomer as gum base, fats, oils, softener, filler, wax, colorant, plasticizer, acidulant, bulking agent, and sweetener (columns 8-10). The composition further comprises medicament (column 6). Cherukuri does not teach chewing the chewing gum, and continuing to chew the chewing gum to create a fluid pressure or saliva content of medicament of approximately 1700 to about 4400 ppm, causing the medicament to absorb through oral mucosa. However, chewing a chewing gum is obvious to one of ordinary skill in the art, and by continuously chewing the chewing gum, it would have been obvious to one of ordinary skill in this at that the medicament release into the saliva is either swallowed or absorbed through the oral mucosa. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to chew or continue chewing the chewing gum to obtain the desirable amount to medicament to achieve a desired effect.

Claims 5, 12, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherukuri et al.

Cherukuri is relied upon for the reason stated above. Cherukuri does not teach chewing the chewing gum at least twice a day. However, it is the position of the examiner that the amounts of medicament being administered are within the capability of the skilled artisan to determine a suitable dosage according to the daily needed basis.

Claims 1, 7, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherukuri et al., and Hausler et al. US 5,922,347.

Cherukuri is relied upon for the reason stated above. Cherukuri does not teach chewing the chewing gum, and continuing to chew the chewing gum to force the medicament to absorb through oral mucosa

Hausler teaches a stable chewing gum formulation comprises active drug (column 2, lines 8-56), filling, emulsifying, waxes, plasticising, and sugar (column 3, lines 11-67). Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to modify Cherukuri's chewing gum composition with the teaching of Hausler to obtain a safe and stable chewing gum containing medicament, which is tolerated by the mucous membrane, because the references teach the advantageous results of medicament chewing gum compositions useful in pharmaceutical art.

Response to Arguments

Applicant's arguments filed 01/30/03 have been fully considered but they are not persuasive.

Applicant argues that Cherukuri teaches the amount of medicament used in general is "the ordinary dosage required to obtain the desired result", and therefore, Cherukuri is clearly teaching away from the present invention where less than the ordinary amount is used. In response to applicant's argument, since applicant has not defined the "typical amount", the examiner cannot establish the patentability distinct between "less than a typical amount" and "ordinary amount" disclosed by Cherukuri.

Applicant argues that Cherukuri does not disclose or remotely suggest a method of delivering a medicament which includes the step of chewing gum for at least two

minutes. However, absent of showing evidence on the contrary, it would have been obvious for one of ordinary skill in this art to chew Cherukuri's chewing gum in order to obtain a desired effect of the medicament in the chewing gum.

Applicant argues that Cherukuri is completely silent as to any methods of chewing the chewing gum for at least two minutes to deliver a medicament. Although Cherukuri is silent as to the time of chewing the chewing gum, it is the position of the examiner that it would have been obvious for one of ordinary skill to continue chewing the chewing gum for at least 2 minutes, because Cherukuri teaches a chewing gum composition comprising medicament useful in pharmaceutical art. Therefore, it would have been obvious to the skilled artisan to keep chewing until the desired effect is obtained.

Applicant argues that Hausler does not teach any methods for delivering a medicament in a chewing gum composition that involves using less than the typical amount of agent that is swallowed by an individual, and therefore, Hausler does not remedy the deficiencies of Cherukuri. In response to applicant's argument, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Again, the examiner has not been able to compare "less than a typical amount" and "ordinary amount" taught by Cherukuri and Hausler. Thus, it is the position of the

examiner that no patentability distinct can be seen in the particular limitation, because "less than a typical amount" can be any ordinary amount.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Tran whose telephone number is (703) 306-5816. The examiner can normally be reached on Monday through Thursday from 6:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

UNITED STATES
PATENT AND
TRADEMARK OFFICE

Commissioner for Patents
Washington, DC 20231
www.uspto.gov

FEB 20 2003

Dear Patent Business Customer:

The United States Patent and Trademark Office ("Office") is now permitting and encouraging applicants to voluntarily submit amendments in a revised format as set forth in *AMENDMENTS IN A REVISED FORMAT NOW PERMITTED*, ____ *Off. Gaz. Pat. Office* __ (February 25, 2003), currently available on the USPTO web site at **http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm**. The revised format permits amendments to the specification and claims to be made in a single marked-up version; the requirement for a clean version is eliminated. Attached, you will find a flyer with information and instructions regarding the procedures to be used to comply with the revised format. The flyers are being inserted with out-going Office actions mailed during the period of February 20, 2003 - March 31, 2003.

The revised amendment format is essentially the same as the amendment format for the specification, claims, and drawings that the Office is considering adopting via a revision to 37 CFR 1.121 (Manner of Making Amendments). The revision to 37 CFR 1.121 (if adopted) will simplify amendment submission and improve file management. This proposed revision and others necessary to facilitate a gradual transition to the use of an Electronic File Wrapper (EFW) will be set forth in a Notice of Proposed Rule making (NPR), expected to be published by March 2003. After consideration of public comments, the Office anticipates adopting a revision to § 1.121, following publication of a Notice of Final Rule making (NFR), expected by June 2003, at which point compliance with revised § 1.121 will be mandatory.

The Office will continue to accept your amendment submissions in the revised format during the voluntary period, which will extend up to the effective date of final revisions to § 1.121. The Office also encourages your feedback on the proposed revised amendment format and other changes set forth in the NPR, expected to be published by March 2003.

For assistance: Any questions regarding the submission of amendments pursuant to the revised practice should be directed to Office of Patent Legal Administration (OPLA), Legal Advisors Elizabeth Dougherty (**Elizabeth.Dougherty@uspto.gov**), Gena Jones (**Eugenia.Jones@uspto.gov**) or Joe Narcavage (**Joseph.Narcavage@uspto.gov**). Alternately, you may send e-mail to "Patent Practice", the OPLA e-mail address that has been established for receiving queries and questions about patent practice and procedures or telephone OPLA at (703) 305-1616.

Nicholas P. Godici
Commissioner for Patents

Attachment: Flyer entitled: *Revised Notice* AMENDMENTS MAY NOW BE SUBMITTED IN REVISED FORMAT*

United States Patent [19]

Cherukuri et al.

[11] **Patent Number: 5,013,716**

[45] **Date of Patent: May 7, 1991**

[54] **UNPLEASANT TASTE MASKING COMPOSITIONS AND METHODS FOR PREPARING SAME**

[75] Inventors: **Subraman R. Cherukuri**, Towaco, N.J.; **Lucy L. Wong**, Jackson Heights, N.Y.; **Steven M. Faust**, Stanhope, N.J.

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **264,281**

[22] Filed: **Oct. 28, 1988**

[51] **Int. Cl.**[5] **A61K 31/70**; A61K 31/715

[52] **U.S. Cl.** **514/23**; 514/53; 514/54; 514/819; 514/824; 514/825; 514/853; 514/855; 514/867; 424/48; 424/439; 424/440; 424/441; 426/548; 426/648; 426/650; 426/651; 426/656

[58] **Field of Search** 426/548, 648, 650, 651, 426/656, 658, 660; 424/439, 440, 441, 48; 514/2, 53, 54; 536/18.4, 4.1; 530/801; 524/819, 824, 225, 853, 855, 867

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Primary Examiner—John W. Rollins

Attorney, Agent, or Firm—Craig M. Bell

[57] **ABSTRACT**

The present invention pertains to an unpleasant taste masking composition which comprises a flavoring agent having a bitter taste or unpleasant off-note and a sufficient amount of a non-bitter intense sweetener to nullify the taste or off-note of the flavoring agent. The unpleasant taste masking composition may be used in ingestible products such as hard and soft confections, chewing gum compositions and the like. The present invention also pertains to a method for preparing the unpleasant taste masking compositions and the ingestible products in which they may be used.

31 Claims, No Drawings

UNPLEASANT TASTE MASKING COMPOSITIONS AND METHODS FOR PREPARING SAME

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to unpleasant taste masking compositions prepared by combination of a non-bitter intense sweetening agent and a flavoring agent having a bitter taste or unpleasant off-note. More particularly, this invention relates to an unpleasant taste masking effect found between the combination of a non-bitter intense sweetening agent such as derivatives of chlorodeoxysugars or dipeptide based sweeteners and a flavoring agent having a bitter taste or unpleasant off-note. The unpleasant taste masking composition may be utilized in a wide variety of ingestible compositions. This invention also relates to methods by which these unpleasant taste masking compositions may be prepared.

2. Description of the Prior Art

"Flavor" is defined as "the simultaneous physiological and psychological response obtained from a substance in the mouth that includes the senses of taste (salty, sour, bitter, sweet), smell (fruity, pungent), and feel . . . [which may be defined as] the effect of chemical action on the mouth membranes such as heat from pepper, coolness from peppermint and the like." Hawley's Condensed Chemical Dictionary, p. 527, 11th Edition (1987). Hence, the perception of flavor involves the interrelationship of many elements. This interrelationship of elements may vary from individual to individual and hence may result in individual perceptions of flavor. The term "flavor", or flavoring agents, is also used to categorize substances which contribute to the taste of an ingestible product. The term "sweetening agent" is used to identify a natural or synthetic food additive which provides sweetness to a food or beverage and which is perceived by the sense of taste. Although the individual perception of flavoring agents and sweetening agents depends on the interrelation of many elements, flavor and sweetness may also be perceived separately, i.e., flavor and sweetness perception may be both dependent upon each other and independent of each other. For example, when a large amount of a flavoring agent is used, a small amount of a sweetening agent may be readily perceptible and vice versa. Thus, the oral interaction between a flavoring agent and a sweetening agent also involves the interrelationship of many elements which may vary from individual to individual and may be a unique sensory sensation.

Intense sweetening agents are natural or synthetic compounds which have a sweetening intensity greater than that of sugar (sucrose) and which oftentimes have a lower caloric value than that of sugar. Because the intense sweeteners provide greater sweetening capacity than sugar, smaller amounts of the sweeteners will provide sweetening intensity equivalent to larger amounts of sugar. Intense sweeteners are well known in the art and are widely used in place of sugar in many low calorie and/or noncariogenic compositions. Intense sweeteners which are not non-caloric, that is, have a caloric value, can provide compositions which have decreased caloric value, as compared to sugarsweetened compositions, because far lower amounts of the intense sweetener are required to achieve optimum sweetness in the composition.

Intense sweeteners have a wide range of chemically distinct structures and, hence, possess varying properties. These intense sweetener compounds include proteins such as thaumatin (Talin, a commercially available product of Tate & Lyle Products, Reading, United Kingdom), dipeptides such as N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester (Aspartame, a commercially available product of the Nutrasweet Company, Deerfield, Ill.) and dihydrochalcones. Each of these compounds has a distinct sweetening intensity as compared to sucrose and this sweetening intensity is well documented. For example, the following compounds have these different sweetening intensities:

Compound	Intensity (compared to sucrose)
Soluble saccharin salts	300×
Cyclamate salts	30×
N-L-alpha-Aspartyl-L-phenylalanine 1-methyl ester (Aspartame)	180×
Potassium salt of 6-methyl-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide (Acesulfame-K, a commercially available product of Hoechst Celanese Corporation, Somerville, New Jersey)	200×
4,1',6'-Trichloro-4,1',6'-trideoxy-galactosucrose (Sucralose, a commercially available product of McNeil Specialty Products Company, Skillman New Jersey)	600×
L-alpha-Aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate (Alitame, a commercially available product of Pfizer, New York, New York)	2000×

Because each intense sweetener is chemically distinct, each sweetener presents a different challenge with respect to the actual use of such sweetener in ingestible compositions. For example, some intense sweeteners present stability problems, such as Aspartame, which exhibits instability in the presence of aldehydes, ketones, moisture and the like. Other intense sweeteners have an associated bitter taste or off-note, such as Saccharin (a commercially available product of PMC Specialty Group Inc., Cinncinnati, Ohio), stevioside, Acesulfame-K , glycyrrhizin, dipotassium glycyrrhizin, glycyrrhizic acid ammonium salt, and thaumatin (Talin).

Certain intense sweeteners have been used to offset the associated bitter aftertaste or unpleasant offnote of other intense sweeteners. For example, United Kingdom patent application no. 2154850A, assigned to Tate & Lyle plc, discloses the use of a combination of at least two intense sweeteners to modify the associated unpleasant taste of one of the sweeteners (cyclamate). The combination of the two sweeteners is said to provide a preferred sweetness. Specifically, a composition is disclosed for sweetening a beverage such as a cola, tea or coffee which comprises combining a chlorosucrose sweetener with a cyclamate, which is either alone or is in combination with other sweeteners.

U.S. Pat. No. 4,495,170, issued to Beytes et al. and assigned to Tate and Lyle plc, discloses synergistic sweetening compositions which comprise a mixture of a chlorodeoxysugar and another sweetening agent which has an associated bitter taste. The chlorodeoxysugars are selected from the group consisting of chlorodeoxysucroses and chlorodeoxygalactosucroses. The bitter

tasting sweetening agent is selected from the group consisting of Saccharin, stevioside and Acesulfame-K.

U.S. Pat. No. 4,535,396, issued to Stephens, Jr. et al. and assigned to Pfizer Inc., teaches a method of masking the bitter taste and enhancing the sweet taste of Acesulfame-K by combining the bitter-tasting intense sweetener with the sweetener Alitame.

U.S. Pat. No. 4,158,068, issued to Von Rymon Lipinski et al. and assigned to Hoechst (West Germany), discloses a sweetener mixture to improve the saccharose-like quality of acetosulfame-K. Specifically, acetosulfame-K is combined with at least one intense sweetener selected from the group consisting of aspartyl peptide ester sweeteners, sulfamate sweeteners, sulfimide sweeteners and dihydrochalcone sweeteners.

Thus, a variety of combinations of intense sweeteners are known which provide compositions which have a reduced associated bitter taste or other unpleasant off-note. However, intense sweeteners which have an associated bitter taste or unpleasant off-note are known to increase the unpleasant taste of compositions containing certain flavors. Accordingly, there is a need for bitterness or off-note masking compositions which mask ingestible compositions which contain flavoring agents having a bitter taste or unpleasant off-note. Such unpleasant taste masking compositions would provide an improved taste for a prolonged period of time for ingestible compositions which contain flavors having a bitter taste or unpleasant off-note, would allow for a reduced total amount of sweetening composition, would thereby reduce costs, stability problems, cariogenic properties, and the like. The present invention provides such unpleasant taste masking compositions and various ingestible compositions which incorporate such unpleasant taste masking compositions.

SUMMARY OF THE INVENTION

The present invention pertains to an unpleasant taste masking composition which comprises a flavoring agent having a bitter taste or unpleasant off-note and a sufficient amount of a non-bitter intense sweetener to nullify the bitter taste or unpleasant off-note of the flavoring agent. The unpleasant taste masking composition may be used in ingestible products such as hard and soft confections, chewing gum compositions and the like. The present invention also pertains to methods for preparing the unpleasant taste masking compositions and the ingestible products in which they may be used.

DETAILED DESCRIPTION OF THE INVENTION

The present invention pertains to compositions which contain certain non-bitter intense sweeteners which mask the bitterness or off-note of certain flavors. In particular, the present invention pertains to a combination of a flavoring agent having a bitter taste or unpleasant off-note and a sufficient amount of a non-bitter intense sweetening agent such as a chlorodeoxysugar derivative or a dipeptide based sweetener to nullify the bitter taste or unpleasant off-note of the flavoring agent. The present invention provides unpleasant taste masking compositions which have an improved taste without a bitter or off-note for a prolonged period of time, as well as ingestible products which contain the unpleasant taste masking compositions.

By the term "ingestible", applicants include all materials and compositions which are used by, or which perform a function in, the body. Thus, materials and compositions which are not adsorbed or absorbed are included as well as digestible and non-digestible materials and compositions.

In a preferred embodiment, the unpleasant taste masking compositions comprise in percentages by weight (1) a flavoring agent having a bitter taste or unpleasant off-note in an amount from about 0.0001% to about 5.0%, and (2) an intense sweetening agent present in an amount from about 0.001% to about 5.0%. In a more preferred embodiment, the unpleasant taste masking compositions comprise in percentages by weight (1) a flavoring agent having a bitter taste or unpleasant off-note in an amount from about 1.0% to about 3.0%, and (2) an intense sweetening agent present in an amount from about 0.02% to about 1.0%. In a most preferred embodiment, the unpleasant taste masking compositions comprise in percentages by weight (1) a flavoring agent having a bitter taste or unpleasant off-note in an amount from about 1.2% to about 2.5%, and (2) an intense sweetening agent present in an amount from about 0.05% to about 0.5%.

The non-bitter intense sweetening agents (sweeteners) of the present invention may be chlorodeoxysugar derivatives or dipeptide based sweeteners. The chlorodeoxysugar derivatives may be derivatrves of chlorodeoxysucrose or chlorodeoxygalactosucrose. Examples of chlorodeoxysucrose and chlorodeoxygalactosucrose derivatives include but are not limited to:

(a) 1-chloro-1'-deoxysucrose;
(b) 4-chloro-4-deoxy-alpha-D-galactopyranosyl-alpha-D-fructofuranoside, or 4-chloro-4-deoxygalactosucrose;
(c) 4-chloro-4-deoxy-alpha-D-galactopyranosyl-1-chloro-1-deoxy-beta-D-fructofuranoside, or 4,1'-dichloro-4,1'-dideoxygalactosucrose;
(d) 1',6'-dichloro-1',6'-dideoxysucrose;
(e) 4-chloro-4-deoxy-alpha-D-galactopyranosyl-1,6-dichloro-1,6-dideoxy-beta-D-fructofuranoside, or 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose;
(f) 4,6-dichloro-4,6-dideoxy-alpha-D-galacto-pyranosyl-6-chloro-6-deoxy-beta-D-fructofuranoside, or 4,6,6'-trichloro-4,6,6'-trideoxygalactosucrose;
(g) 6,1',6'-trichloro-6,1',6'-trideoxysucrose;
(h) 4,6-dichloro-4,6-dideoxy-alpha-D-galacto-pyranosyl-1,6-dichloro-1,6-dideoxy-beta-D-fructofuranoside, or 4,6,1',6'-tetrachloro-4,6,1',6'-tetradeoxygalactosucrose; and
(i) 4,6,1',6'-tetrachloro-4,6,1',6'-tetradeoxysucrose.

In a preferred embodiment, the chlorodeoxysugar derivative is 4-chloro-4-deoxy-alpha-D-galactopyranosyl-1,6-dichloro-1,6-dideoxy-beta-D-fructofuranoside, which is also known as 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose (Sucralose).

The non-bitter intense sweeteners of the present invention may also be dipeptide based sweeteners. Examples of dipeptide based sweeteners which may be used include but are not limited to:

(a) N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester (Aspartame);
(b) L-alpha-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate (Alitame);
(c) methyl esters of L-aspartyl-L-phenylglycerine;
(d) methyl esters of L-aspartyl-L-2,5-dihydrophenylglycine;
(e) L-aspartyl-2,5-dihydro-L-phenylalanine; and
(f) L-aspartyl-L-(1-cyclohexen)-alanine.

See also, Mazur et al., *J. Amer. Chem. Soc.*, 91, 10 (1969), *Structure-Taste Relationships of Some Dipeptides.*

In a preferred embodiment, the dipeptide based sweetener is N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester (Aspartame). In an alternative preferred embodiment, the dipeptide based sweetener is L-alpha-aspartyl-N(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate (Alitame).

The non-bitter intense sweetener of the present invention may be used in many distinct physical forms well known in the art to provide an initial burst of sweetness and flavor and/or a prolonged sensation of sweetness and flavor. Without being limited thereto, such physical forms include free forms, such as spray dried, powdered, and beaded forms, and encapsulated forms, and mixtures thereof.

The amount of non-bitter intense sweetening agent employed herein is that amount sufficient to nullify the bitter taste or unpleasant off-note of the flavoring agent having a bitter or unpleasant off-note. The amount of nonbitter intense sweetening agent employed is normally a matter of preference subject to such factors as the individual intense sweetener, the individual flavoring agent having a bitter or unpleasant off-note, the type of bulking agent or carrier employed, and the strength of sweetness and flavor desired. Thus the amount of sweetener may be varied in order to obtain the result desired in the final product and such variations are within the capabilities of those skilled in the art without the need for undue experimentation.

The flavoring agents (flavors, flavorings) of the present invention are flavors having an associated bitter taste or aftertaste or other unpleasant off-note which include those flavors known to the skilled artisan. These flavoring agents having a bitter or unpleasant off-note include natural, artificial and synthetic flavor oils and flavoring aromatics and/or oils, oleoresins and extracts derived from plants, leaves, flowers, fruits, and so forth, and combinations thereof. Nonlimiting representative flavor oils include spearmint oil, peppermint oil, eucalyptus oil, oil of nutmeg, allspice, mace, oil of bitter almonds, menthol and the like. Also useful flavorings are artificial, natural and synthetic fruit flavors such as citrus oils including lemon, orange, lime, grapefruit, and fruit essences including apricot and so forth. These flavoring agents may be used in liquid or solid form and may be used individually or in admixture.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral, i.e., alpha-citral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanal (green fruit), and 2-dodecenal (citrus, mandarin), mixtures thereof and the like.

In a preferred embodiment, the flavoring agent having a bitter or unpleasant off-note is spearmint oil.

The flavoring agent may be employed in either liquid form and/or dried form. When employed in the latter form, suitable drying means such as spray drying the oil may be used. Alternatively, the flavoring agent may be absorbed onto water soluble materials, such as cellulose, starch, sugar, maltodextrin, gum arabic and so forth or may be encapsulated. The actual techniques for preparing such dried forms are well known and do not constitute a part of this invention.

The flavoring agent of the present invention may be used in many distinct physical forms well known in the art to provide an initial burst of flavor and/or a prolonged sensation of flavor. Without being limited thereto, such physical forms include free forms, such as spray dried, powdered, and beaded forms, and encapsulated forms, and mixtures thereof.

The amount of flavoring agent having a bitter or unpleasant off-note employed herein is normally a matter of preference subject to such factors as the individual flavor, the type of bulking agent or carrier employed, and the strength of flavor desired. Thus the amount of flavoring may be varied in order to obtain the result desired in the final product and such variations are within the capabilities of those skilled in the art without the need for undue experimentation.

In addition to the flavoring agents having a bitter or unpleasant off-note, set out above, the present invention also includes the combination of a medicament drug or a pharmaceutical which has a bitter taste or unpleasant off-note and a sufficient amount of a non-bitter intense sweetening agent to nullify the bitter taste or unpleasant off-note of the medicament.

The medicament drugs (medicaments, pharmaceuticals) of the present invention may be selected from a wide variety of drugs and their acid addition salts. Both organic and inorganic salts may be used provided the drug maintains its medicament value. Exemplary acid salts include hydrochloride, hydrobromide, orthophosphate, benzoate, maleate, tartrate, succinate, citrate, salicylate, sulfate and acetate.

The medicament drug may be selected from a wide range of unpleasant tasting therapeutic agents and mixtures of therapeutic agents. Nonlimiting illustrative categories and specific examples include:

(a) Analgesics, such as acetaminophen, ibuprofen, phenactetin and salicylamide;

(b) Antiasmatics, such as amino-phylline, metaproterenol, epinephrine and theophylline;

(c) Antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate and chlophedianol hydrochloride;

(d) Antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, phenyltoloxamine citrate, diphenylhydramine hydrochloride, promethazine and triprolidine;

(e) Antinauseants, such as dimenhydrinate and meclizine;

(f) Decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride and ephedrine;

(g) Various alkaloids, such as codeine phosphate, codeine sulfate and morphine;

(h) Laxatives, such as phenolphthalein, danthron, pamabrom and bisocadyl;

(i) Anticholesterolemic and antilipid agents, such as gemfibrozil;

(j) Appetite suppressants, such as phenylpropanolamine hydrochloride and caffeine;

(k) Central nervous system stimulants, such as nicotine;

(l) Expectorants, such as guaifenesin;

(m) Anti-inflammatory agents, such as isoxicam, meclophenamic acid and naproxen; and

(n) Nutritional supplements, including vitamins and minerals, such as niacin, pantothenic acid, vitamin B6, thiamine hydrochloride, riboflavin, potassium iodide, potassium chloride-, cupric sulfate and ferrous sulfate.

In a preferred embodiment the medicament is selected from the group consisting of dextromethorphan, dextromethorphan hydrobromide, pseudoephedrine,

pseudoephedrine hydrochloride, guaifenesin and mixtures thereof.

The medicament of the present invention may be used in many distinct physical forms well known in the pharmaceutical art to provide an initial dosage of the medicament and/or a time-release form of the medicament. Without being limited thereto, such physical forms include free forms and encapsulated forms, and mixtures thereof.

The amount of medicament drug or its acid addition salt used in the present invention may vary depending upon the therapeutic dosage recommended or permitted. In general, the amount of medicament present is the ordinary dosage required to obtain the desired result. Such dosages are known to the skilled practitioner in the medical arts and is not a part of the present invention.

The unpleasant taste masking compositions of the present invention are prepared by admixing the flavoring agent which has a bitter or unpleasant off-note into the non-bitter intense sweetening agent.

The combination of the non-bitter intense sweeteners and the flavoring agent and/or medicament having a bitter taste or other unpleasant off-note, set out above, in the proportions disclosed, results in an unpleasant taste masking composition having a sweetening effect with no bitter or off-note. The unpleasant taste masking composition of the present invention is markedly greater than that of compositions which contain other intense sweeteners which have an associated bitter or off-note taste. Accordingly, applicants, unpleasant taste masking compositions have the advantage of providing an improved taste over a prolonged period of time.

Once prepared, the inventive unpleasant taste masking composition may be stored for future use or may be formulated with conventional additives, such as pharmaceutically acceptable carriers or confectionery ingredients to prepare a wide variety of ingestible compositions, such as foodstuffs, beverages, jellies, extracts, confectionery products, pharmaceutical compositions administered orally, and hygienic products such as a toothpastes, dental lotions, chewing gums or mouth washes.

The present invention extends to methods of making the ingestible compositions. In such a method, a composition is made by admixing the unpleasant taste masking composition of the present invention with the other ingredients of the final desired composition. Other ingredients will usually be incorporated into the composition as dictated by the nature of the desired composition as well known to those of ordinary skill in the art. The ultimate ingestible compositions are readily prepared using methods generally known in the food technology and pharmaceutical arts.

An important aspect of the present invention includes a chewing gum composition incorporating the inventive unpleasant taste masking composition and a method for preparing the chewing gum composition, including both chewing gum and bubble gum formulations. With regard to a chewing gum composition, such compositions contain a gum base, the inventive unpleasant taste masking composition, and various additives.

The gum base employed will vary greatly depending upon various factors such as the type of base desired, the consistency of gum desired and the other components used in the composition to make the final chewing gum product. The gum base may be any water-insoluble gum base known in the art, and includes those gum bases utilized for chewing gums and bubble gums. Illustrative examples of suitable polymers in gum bases include both natural and synthetic elastomers and rubbers. For example, those polymers which are suitable as gum bases include, without limitation, substances of vegetable origin such as chicle, crown gum, nispero, rosadinha, jelutong, perillo, niger gutta, tunu, balata, gutta-percha, lechi-capsi, sorva, gutta kay, mixtures thereof and the like. Synthetic elastomers such as butadiene-styrene copolymers, polyisobutylene, isobutyleneisoprene copolymers, polyethylene, mixtures thereof and the like are particularly useful.

The gum base may include a non-toxic vinyl polymer, such as polyvinyl acetate and its partial hydrolysate, polyvinyl alcohol, and mixtures thereof. When utilized, the molecular weight of the vinyl polymer may range from about 3,000 up to and including about 94,000.

The amount of gum base employed will vary greatly depending upon various factors such as the type of base used, the consistency of the gum desired and the other components used in the composition to make the final chewing gum product. In general, the gum base will be present in amounts from about 5% to about 94%, by weight of the final chewing gum composition, and preferably in amounts from about 15% to about 45%, and more preferably in amounts from about 15% to about 35%, and most preferably in amounts from about 20% to about 30%, by weiqht of the final chewing gum composition.

The gum base composition may contain conventional elastomer solvents to aid in softening the elastomer base component. Such elastomer solvents may comprise terpinene resins such as polymers of alpha-pinene or beta-pinene, methyl, glycerol or pentaerythritol esters of rosins or modified rosins and gums, such as hydrogenated, dimerized or polymerized rosins or mixtures thereof. Examples of elastomer solvents suitable for use herein include the pentaerythritol ester of partially hydrogenated wood or gum rosin, the pentaerythritol ester of wood or gum rosin, the glycerol ester of wood rosin, the glycerol ester of partially dimerized wood or gum rosin, the glycerol ester of polymerized wood or gum rosin, the glycerol ester of tall oil rosin, the glycerol ester of wood or gum rosin and the partially hydrogenated wood or gum rosin and the partially hydrogenated methyl ester of wood or rosin, mixtures thereof, and the like. The elastomer solvent may be employed in amounts from about 5.0% to about 75.0%, by weight of the gum base, and preferably from about 45.0% to about 70.0%, by weight of the gum base.

A variety of traditional ingredients may be included in the gum base in effective amounts such as plasticizers or softeners such as lanolin, palmitic acid, oleic acid, stearic acid, sodium stearate, potassium stearate, glyceryl triacetate, glyceryl lecithin, glyceryl monostearate, propylene glycol monostearate, acetylated monoglyceride, glycerine, mixtures thereof, and the like may also be incorporated into the gum base to obtain a variety of desirable textures and consistency properties. Waxes, for example, natural and synthetic waxes, hydrogenated vegetable oils, petroleum waxes such as polyurethane waxes, polyethylene waxes, paraffin waxes, microcrystalline waxes, fatty waxes, sorbitan monostearate, tallow, propylene glycol, mixtures thereof, and the like may also be incorporated into the gum base to obtain a variety of desirable textures and consistency properties. These traditional additional materials are generally employed in amounts up to about 30.0%, by weight of the

gum base, and preferably in amounts from about 3% to about 20%, by weight of the gum base.

The gum base may include effective amounts of mineral adjuvants such as calcium carbonate, magnesium carbonate, alumina, aluminum hydroxide, aluminum silicate, talc, tricalcium phosphate, dicalcium phosphate and the like as well as mixtures thereof. These mineral adjuvants may serve as fillers and textural agents. These fillers or adjuvants may be used in the gum base in various amounts. Preferably the amount of filler when used will be present in an amount from greater than about 0% to about 60%, by weight of the chewing gum base.

The chewing gum base may additionally include the conventional additives of coloring agents, antioxidants, preservatives and the like. For example, titanium dioxide and other dyes suitable for food, drug and cosmetic applications, known as F.D. & C. dyes, may be utilized. An anti-oxidant such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, and mixtures thereof, may also be included. Other conventional chewing gum additives known to one having ordinary skill in the chewing gum art may also be used in the chewing gum base.

The gum composition may include effective amounts of conventional additives selected from the group consisting of sweetening agents (sweeteners), plasticizers, softeners, emulsifiers, waxes, fillers, bulking agents, mineral adjuvants, flavoring agents (flavors, flavorings), coloring agents (colorants, colorings), antioxidants, acidulants, thickeners, mixtures thereof and the like. Some of these additives may serve more than one purpose. For example, in sugarless gum compositions, the sweetener, e.g., sorbitol or other sugar alcohol or mixtures thereof, may also function as a bulking agent. Similarly, in sugar containing gum compositions, the sugar sweetener can also function as a bulking agent.

The plasticizers, softeners, mineral adjuvants, colorants, waxes and antioxidants discussed above as being suitable for use in the gum base may also be used in the gum composition. Examples of other conventional additives which may be used include emulsifiers, such as lecithin and glyceryl monostearate, thickeners, used alone or in combination with other softeners, such as methyl cellulose, alginates, carrrageenan, xanthan gum, gelatin, carob, tragacanth, locust bean, and carboxy methyl cellulose, acidulants such as malic acid, adipic acid, citric acid, tartaric acid, fumaric acid, and mixtures thereof, and fillers, such as those discussed above under the category of mineral adjuvants. The fillers when used may be utilized in an amount from greater than about 0% to about 60%, by weight of the gum composition.

Bulking agents (carriers, extenders) suitable for use include sweetening agents selected from the group consisting of monosaccharides, disaccharides, polysaccharides, sugar alcohols, and mixtures thereof; polydextrose; maltodextrins; minerals, such as calcium carbonate, talc, titanium dioxide, dicalcium phosphate, and the like. Bulking agents may be used in amounts up to about 90%, by weight of the final gum composition, with amounts from about 40% to about 70%, by weight of the gum composition being preferred , with from about 50% to about 65%, by weight, being more preferred and from about 55% to about 60%, by weight of the chewing gum composition, being most preferred.

The sweetening agent used may be selected from a wide range of materials including water-soluble sweeteners, water-soluble artificial sweeteners, water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, dipeptide based sweeteners, and protein based sweeteners, including mixtures thereof. Without being limited to particular sweeteners, representative categories and examples include:

(a) water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribulose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, glycyrrhizin, and sugar alcohols such as sorbitol, mannitol, maltitol, hydrogenated starch hydrolysates and mixtures thereof;

(b) water-soluble artificial sweeteners such as soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (Acesulfame-K), the free acid form of saccharin, and the like;

(c) dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (Aspartame) and materials described in U.S. Pat. No. 3,492,131, L-alpha-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate (Alitame), methyl esters of L-aspartyl-L-phenylglycerine and L-aspartyl-L-2,5-dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine; L-aspartyl-L-(1-cyclohexen)-alanine, and the like;

(d) water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as chlorinated derivatives of ordinary sugar (sucrose), known, for example, under the product designation of Sucralose; and

(e) protein based sweeteners such as thaumaoccous danielli (Thaumatin I and II).

In general, an effective amount of sweetener is utilized to provide the level of bulk and/or sweetness desired, and this amount will vary with the sweetener selected. This amount of sweetener will normally be present in amounts from about 0.0025% to about 90%, by weight of the gum composition, depending upon the sweetener used. The exact range of amounts for each type of sweetener is well known in the art and is not the subject of the present invention. The amount of sweetener ordinarily necessary to achieve the desired level of sweetness is independent from the flavor level achieved from flavor oils.

Preferred sugar based-sweeteners are sugar (sucrose), corn syrup and mixtures thereof. Preferred sugarless sweeteners are the sugar alcohols, artificial sweeteners, dipeptide based sweeteners and mixtures thereof. Preferably, sugar alcohols are used in the sugarless compositions because these sweeteners can be used in amounts which are sufficient to provide bulk as well as the desired level of sweetness. Preferred sugar alcohols are selected from the group consisting of sorbitol, xylitol, maltitol, mannitol, and mixtures thereof. More preferably, sorbitol or a mixture of sorbitol and mannitol is utilized. The gamma form of sorbitol is preferred. An artificial sweetener or dipeptide based sweetener is preferably added to the gum compositions which contain sugar alcohols.

The coloring agents useful in the present invention are used in amounts effective to produce the desired color. These coloring agents include pigments which

may be incorporated in amounts up to about 6%, by weight of the gum composition. A preferred pigment, titanium dioxide, may be incorporated in amounts up to about 2%, and preferably less than about 1%, by weight of the composition. The colorants may also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as F.D.& C. dyes and lakes. The materials acceptable for the foregoing uses are preferably water-soluble. Illustrative nonlimiting examples include the indigoid dye known as F.D.& C. Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as F.D.& C. Green No. 1 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-(N-ethyl-p-sulfoniumbenzylamino) diphenylmethylene]-[1-(N-ethyl-N-p-sulfoniumbenzyl)-delta-2,5-cyclohexadieneimine]. A full recitation of all F.D.& C. colorants and their corresponding chemical structures may be found in the KirkOthmer Encyclopedia of Chemical Technology, 3rd Edition, in volume 5 at pages 857–884, which text is incorporated herein by reference.

Suitable oils and fats usable in gum compositions include partially hydrogenated vegetable or animal fats, such as coconut oil, palm kernel oil, beef tallow, lard, and the like. These ingredients when used are generally present in amounts up to about 7.0%, by weight, and preferably up to about 3.5%, by weight of the gum composition.

In accordance with this invention, effective amounts of the unpleasant taste masking compositions of the present invention may be admixed into the chewing gum composition. The amount of unpleasant taste masking composition employed is normally a matter of preference subject to such factors as the individual flavor having a bitter or unpleasant off-note, the type of bulking agent or carrier employed, the type of non-bitter intense sweetener used and the strength of flavor desired. In addition, in the case of a medicated chewing gum product containing a medicament, the amount of unpleasant taste masking composition employed is subject to such additional factors as the degree of bitter or off-note taste of the medicament and the therapeutically effective dosage level of the medicament. Thus, the amount of unpleasant taste masking composition may be varied in order to obtain the result desired in the final product and such variations are within the capabilities of those skilled in the art without the need for undue experimentation.

In a preferred embodiment, the unpleasant taste masking compositions comprise in percentages by weight (1) a flavoring agent having a bitter taste or unpleasant off-note in an amount from about 0.0001% to about 5.0%, and (2) an intense sweetening agent present in an amount from about 0.001% to about 5.0%. In a more preferred embodiment, the unpleasant taste masking compositions comprise in percentages by weight (1) a flavoring agent having a bitter taste or unpleasant off-note in an amount from about 1.0% to about 3.0%, and (2) an intense sweetening agent present in an amount from about 0.02% to about 1.0%. In a most preferred embodiment, the unpleasant taste masking compositions comprise in percentages by weight (1) a flavoring agent having a bitter taste or unpleasant off-note in an amount from about 1.2% to about 2.5%, and (2) an intense sweetening agent present in an amount from about 0.05% to about 0.5%.

In addition to the inventive unpleasant taste masking compositions containing a flavoring agent having a bitter or other unpleasant off-note, secondary flavoring agents may also be used in the chewing gum formulations of this invention. Such additional flavors should be compatible with the unpleasant taste masking composition and not adversely alter the sensory perception of the unpleasant taste masking composition.

The secondary flavoring agents useful to prepare the flavoring compositions of this invention include those flavorings known to the skilled artisan such as flavorings derived from plants, leaves, flowers, fruits, and the like, and mixtures thereof. Representative flavor oils include cinnamon oil and oil of wintergreen (methyl salicylate). Also useful flavorants are artificial, natural and synthetic fruit flavors such as citrus oils, including lemon, lime, orange, grape, and grapefruit, and fruit essences including apple, strawberry, cherry, pineapple and the like, and mixtures thereof.

The secondary flavoring agent may be employed in either liquid form and/or dried form. When employed in the latter form, suitable drying means such as spray drying the oil may be used. Alternatively, the secondary flavoring agent may be absorbed onto water soluble materials, such as cellulose, starch, sugar, maltodextrin, gum arabic and so forth. The actual techniques for preparing such dried forms are well known and do not constitute a part of this invention.

The secondary flavoring agents of the present invention may be used in many distinct physical forms well known in the art to provide an initial burst of flavor and/or a prolonged sensation of flavor. Without being limited thereto, such physical forms include free forms, such as spray dried, powdered, and beaded forms, and encapsulated forms, and mixtures thereof.

The amount of secondary flavoring agent employed in the chewing gum composition of this invention is normally a matter of preference. In general, the secondary flavoring agent is present in amounts from about 0.02% to about 5%, by weight of the gum composition. Preferably, the secondary flavoring agent is present in amounts from about 0.1% to about 2%, by weight, and more preferably, the secondary flavoring agent is present in amounts from about 0.3% to about 1.5%, by weight of the chewing gum composition.

The unpleasant taste masking compositions may be incorporated into an otherwise conventional chewing gum composition using standard techniques and equipment known to those skilled in the art. For example, a gum base is heated to a temperature sufficiently high enough to soften the base without adversely effecting the physical and chemical make up of the base. The optimum temperatures utilized may vary depending upon the composition of the gum base used, but such temperatures are readily determined by those skilled in the art without undue experimentation.

The gum base is conventionally melted at temperatures that range from about 60° C. to about 120° C. for a period of time sufficient to render the base molten. For example, the gum base may be heated under these conditions for a period of about thirty minutes just prior to being admixed incrementally with the remaining ingredients of the base such as the plasticizer, fillers, the bulking agent and/or sweeteners, the softener and coloring agents to plasticize the blend as well as to modulate the hardness, viscoelasticity and formability of the base. The chewing gum base is then blended with the flavoring agents having a bitter taste or unpleasant off-note and intense sweeteners of the unpleasant taste masking composition which may have been previously

blended with other traditional ingredients. Mixing is continued until a uniform mixture of gum composition is obtained. Thereafter the gum composition mixture may be formed into desirable chewing gum shapes.

The preparation of confectionery formulations is historically well known and has changed little through the years. Confectionery items have been classified as either "hard" confectionery or "soft" confectionery. The unpleasant taste masking compositions of the present invention can be incorporated by admixing the inventive composition into conventional hard and soft confections.

Hard confectionery may be processed and formulated by conventional means. In general, a hard confectionery has a base composed of a mixture of sugar and other carbohydrate bulking agents kept in an amorphous or glassy condition. This form is considered a solid syrup of sugars generally having from about 0.5% to about 1.5% moisture. Such materials normally contain up to about 92% corn syrup, up to about 55% sugar and from about 0.1% to about 5% water, by weight of the final composition. The syrup component is generally prepared from corn syrups high in fructose, but may include other materials. Further ingredients such as flavorings, sweeteners, acidulants, colorants and so forth may also be added.

Such confectionery may be routinely prepared by conventional methods such as those involving fire cookers, vacuum cookers, and scraped-surface cookers also referred to as high speed atmospheric cookers.

Fire cookers involve the traditional method of making a candy base. In this method, the desired quantity of carbohydrate bulking agent is dissolved in water by heating the agent in a kettle until the bulking agent dissolves. Additional bulking agent may then be added and cooking continued until a final temperature of 145° to 156° C. is achieved. The batch is then cooled and worked as a plastic-like mass to incorporate additives such as flavors, colorants and the like.

A high-speed atmospheric cooker uses a heatexchanger surface which involves spreading a film of candy on a heat exchange surface, the candy is heated to 165° to 170° C. in a few minutes. The candy is then rapidly cooled to 100° to 120° C. and worked as a plastic-like mass enabling incorporation of the additives, such as flavors, colorants and the like.

In vacuum cookers, the carbohydrate bulking agent is boiled to 125° to 132° C., vacuum is applied and additional water is boiled off without extra heating. When cooking is complete, the mass is a semi-solid and has a plastic-like consistency. At this point, flavors, colorants, and other additives are admixed in the mass by routine mechanical mixing operations.

The optimum mixing required to uniformly mix the flavors, colorants and other additives during conventional manufacturing of hard confectionery is determined by the time needed to obtain a uniform distribution of the materials. Normally, mixing times of from 4 to 10 minutes have been found to be acceptable.

Once the candy mass has been properly tempered, it may be cut into workable portions or formed into desired shapes. A variety of forming techniques may be utilized depending upon the shape and size of the final product desired. A general discussion of the composition and preparation of hard confections may be found in H. A. Lieberman, *Pharmaceutical Dosage Forms: Tablets*, Volume 1 (1980), Marcel Dekker, Inc., New York, N.Y. at pages 339 to 469, which disclosure is incorporated herein by reference.

The apparatus useful in accordance with the present invention comprises cooking and mixing apparatus well known in the confectionery manufacturing arts, and therefore the selection of the specific apparatus will be apparent to the artisan.

In contrast, compressed tablet confections contain particular materials and are formed into structures under pressure. These confections generally contain sugars in amounts up to about 95%, by weight of the composition, and typical tablet excipients such as binders and lubricants as well as flavors, colorants and so forth.

Similar to hard confectionery, soft confectionery may be utilized in this invention. The preparation of soft confections, such as nougat, involves conventional methods, such as the combination of two primary components, namely (1) a high boiling syrup such as a corn syrup, hydrogenated starch hydrolysate or the like, and (2) a relatively light textured frappe, generally prepared from egg albumin, gelatin, vegetable proteins, such as soy derived compounds, sugarless milk derived compounds such as milk proteins, and mixtures thereof. The frappe is generally relatively light, and may, for example, range in density from about 0.5 to about 0.7 grams/cc.

The high boiling syrup, or "bob syrup" of the soft confectionery is relatively viscous and has a higher density than the frappe component, and frequently contains a substantial amount of carbohydrate bulking agent such as a hydrogenated starch hydrolysate. Conventionally, the final nougat composition is prepared by the addition of the "bob syrup" to the frappe under agitation, to form the basic nougat mixture. Further ingredients such as flavoring, additional carbohydrate bulking agent, colorants, preservatives, medicaments, mixtures thereof and the like may be added thereafter also under agitation. A general discussion of the composition and preparation of nougat confections may be found in B. W. Minifie, *Chocolate, Cocoa and Confectionery*: Science and Technology, 2nd edition, AVI Publishing Co., Inc., Westport, Conn. (1980), at pages 424–425, which disclosure is incorporated herein by reference.

The procedure for preparing the soft confectionery involves known procedures. In general, the frappe component is prepared first and thereafter the syrup component is slowly added under agitation at a temperature of at least about 65° C., and preferably at least about 100° C. The mixture of components is continued to be mixed to form a uniform mixture, after which the mixture is cooled to a temperature below 80o C , at which point, the flavor may be added. The mixture is further mixed for an additional period until it is ready to be removed and formed into suitable confectionery shapes.

In accordance with this invention, effective amounts of the unpleasant taste masking compositions of the present invention may be admixed into the hard and soft confections. The amount of unpleasant taste masking composition employed is normally a matter of preference subject to such factors as the individual flavor having a bitter or unpleasant off-note, the type of bulking agent or carrier employed, and the type of non-bitter intense sweetener used. In addition, in the case of a medicated confectionery product containing a medicament, the amount of unpleasant taste masking composition employed is subject to such additional factors as the

degree of bitter taste or unpleasant off-note of the medicament and the therapeutically effective dosage level of the medicament. Thus the amount of unpleasant taste masking composition may be varied in order to obtain the result desired in the final product and such variations are within the capabilities of those skilled in the art without the need for undue experimentation.

The unpleasant taste masking compositions may be incorporated into an otherwise conventional hard or soft confection composition using standard techniques and equipment known to those skilled in the art.

Also in accordance with this invention, effective amounts of the unpleasant taste masking compositions containing medicaments may be admixed into pharmaceutical ingestible compositions. The amount of unpleasant taste masking composition employed is subject to such factors as the therapeutically effective dosage level of the medicament and the degree of bitter taste or unpleasant off-note of the medicament. Thus the amount of unpleasant taste masking composition may be varied in order to obtain the result desired in the final product and such variations are within the capabilities of those skilled in the art without the need for undue experimentation.

The pharmaceutical ingestible compositions of the invention may be prepared by conventional methods long established in the art of pharmaceutical compounding. The compositions may contain conventional adjuvant materials employed in formulating the compositions of the art. The pharmaceutically acceptable carriers may be selected from a wide range of materials. Without being limited thereto, such materials include diluents, binders and adhesives, lubricants, disintegrants, colorants, flavorings, sweeteners, and miscellaneous materials such as buffers and adsorbents in order to prepare a particular composition.

The unpleasant taste masking compositions may be formulated with conventional ingredients which offer a variety of textures to suit particular applications. Such ingredients may be in the form of hard and soft confections, tablets, toffee, nougat, chewy candy, chewing gum and so forth, both sugar and sugarless. The acceptable ingredients may be selected from a wide range of materials. Without being limited thereto, such materials include diluents, binders and adhesives, lubricants, disintegrants, bulking agents, humectants and buffers and adsorbents. The preparation of such confections and chewing gum products is well known.

The present invention is further illustrated by the following examples which are not intended to limit the effective scope of the claims. All parts and percentages in the examples and throughout the specification and claims are by weight of the final composition unless otherwise specified.

EXAMPLES 1-8

These examples demonstrate unpleasant taste masking ability for various intense sweeteners in chewing gum products containing spearmint oil as the flavoring agent.

EXAMPLES 1-8

Ingredient (Percent by Weight)	EXAMPLES 1	2	3	4	5	6	7	8
gum base	23.0	23.0	23.0	23.0	23.0	23.0	23.0	23.0
bulking agent	60.01	59.95	59.935	59.9	59.8	59.66	59.87	59.76
softener	15.5	15.5	15.5	15.5	15.5	15.5	15.5	15.5
colorant	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
spearmint	1.32	1.32	1.32	1.32	1.32	1.32	1.32	1.32
Sucralose (ppm)	—	525	750	1000				
Aspartame (ppm)	—				2000	3500		
Saccharin (ppm)	—						1400	
Acesulfame-K (ppm)	—							2500

An expert sensory chew panel evaluated the chewing gum products of examples 1-8. Example 1 illustrates a conventional gum product containing spearmint oil as the flavoring agent with no non-bitter intense sweetener present.

The chewing gum products of examples 7 and 8, which contained Saccharin and Acesulfame-K as the intense sweetening agents, respectively, did not exhibit a decrease in bitter sensation or other off-note compared to the chewing gum product of example 1 which contained no intense sweetener. The chewing gum products of examples 2 and 3, which contained small amounts of Sucralose, and the chewing gum products of examples 5 and 6, which contained Aspartame, exhibited an unpleasant taste profile having a 50% reduction in bitterness/off-note sensation compared to the chewing gum product of example 1. The chewing gum product of example 4, which contained twice the amount of Sucralose sweetener as the product of example 2, showed a surprisingly much greater reduction in bitterness/off-note sensation than the chewing gum products of examples 2, 3, 5 and 6.

The chewing gum product of example 4 was significantly more preferred than the other chewing gum products of examples 1-8 because the product of example 4 had a pleasant and prolonged spearmint flavor without any bitter aftertaste or other unpleasant off-note.

EXAMPLES 9-14

These examples demonstrate unpleasant taste masking ability for various intense sweeteners in chewing gum products containing spearmint oil as the flavoring agent.

EXAMPLES 9-14

Ingredient (Percent by Weight)	EXAMPLES 9	10	11	12	13	14
gum base	23.0	23.0	23.0	23.0	23.0	23.0
bulking agent	59.8	59.475	59.7	59.6	59.65	59.55
softener	15.5	15.5	15.5	15.5	15.5	15.5
colorant	0.2	0.2	0.2	0.2	0.2	0.2
spearmint	1.5	1.5	1.5	1.5	1.5	1.5
Sucralose (ppm)	—	525	1000			
Aspartame (ppm)	—			2000		
Saccharin (ppm)	—				1500	
Acesulfame-K (ppm)	—					2500

An expert sensory chew panel evaluated the chewing gum products of examples 9–14. Example 9 illustrates a conventional gum product containing spearmint oil as the flavoring agent (which has a bitter taste or unpleasant offnote) with no non-bitter intense sweetener present. The chewing gum product of example 9 contained a 13.6% increase in spearmint flavor ingredients which resulted in a nearly twofold increase in the bitter/off-note sensation taste of the chewing gum product.

The chewing gum product of examples 13 and 14, which contained Saccharin and Acesulfame-K as the intense sweetening agents, respectively, exhibited little or no reduction of bitterness/or other off-note sensation compared to the chewing gum product of example 9 which contain no intense sweetener. The chewing gum products of examples 10 and 12, which contained small amounts of Sucralose and Aspartame as the intense sweetener, similarly showed little reduction of unpleasant taste compared to the product of example 9. The most significant decrease in the reduction of unpleasant taste/bitterness sensation was observed in the chewing gum product of example 11, which contained twice the amount of Sucralose sweetener as the product of example 10.

The chewing gum product of example 11 was significantly more preferred than the chewing gum products of examples 9–10 and 12–14 because the product of example 11 had a pleasant and prolonged spearmint flavor without any bitter aftertaste or other unpleasant off-note.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

We claim:

1. An unpleasant taste masking composition which comprises a medicament drug having a bitter taste or unpleasant off-note and a chlorodeoxysugar derivative selected from the group consisting of chlorodeoxysucrose derivatives and chlorodeoxygalactosucrose derivaties and mixtures thereof in an amount from about 0.001% to about 5.0%, by weight to nullify the taste or unpleasant off-note of the medicament drug.

2. The composition of claim 1, wherein the chlorodeoxysugar derivative is 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose.

3. The composition of claim 1, wherein the medicament drug having a bitter taste or unpleasant off-note is selected from the group of medicament drugs consisting of analgesics, antiasmatics, antitussives, antihistamines, antinauseants, decongestants, alkaloids, laxatives, anticholesterolemic and antiliped agents, appetite suppressants, central nervous system stimulants, expectorants, anti-inflammatory agents, nutritional supplements and mixtures thereof.

4. The composition of claim 1, wherein the chlorodeoxysugar derivative is present in an amount from about 0.02% to about 1.0%, by weight of the composition.

5. The composition of claim 4 wherein the chlorodeoxysugar derivative is present in an amount from about 0.05% to about 0.5% by weight of the composition.

6. The composition of claim 1, wherein the medicament drug having a bitter taste or unpleasant off-note is present in an amount from about 0.0001% to about 5.0%, by weight of the composition.

7. A chewing gum composition which comprises a chewing gum base and an effective amount of an unpleasant taste masking composition wherein the unpleasant taste masking composition comprises a medicament drug having a bitter taste or unpleasant off-note and a chlorodeoxysugar derivative selected from the group consisting of chlorodeoxysucrose derivatives and chlorodeoxygalactosucrose derivatives and mixtures thereof in an amount from about 0.001% to about 5.0%, by weight to nullify the taste or unpleasant off-note of the medicament drug.

8. The chewing gum composition of claim 7, wherein the chloroeoxysugar derivative is 4,1', 6', -trichloro-4,1',6'-trideoxygalactosucrose.

9. The chewing gum composition of claim 7, wherein the medicament drug having a bitter taste or unplesant off-note is selected from the group of medicament drugs consisting of analgesics, antiasmatics, antitussives, antihistamines, antinauseants, decongestants, alkaloids, laxatives, anticholesterolemic and antiliped agents, appetite suppressants, central nervous system stimulants, expectorants, anti-inflammatory agents, nutritional supplements and mixtures thereof.

10. The chewing gum composition of claim 7, wherein the chlorodeoxysugar derivative is present in ana mount from about 0.02% to about 1.0%, by weight of the composition.

11. The chewing gum composition of claim 10, wherein the chlorodeoxysugar derivative is present in an amount from about 0.05% to about 0.5% by weight of the composition.

12. A chewing gum composition which comprises a chewing gum base and an effective amount of an unpleasant taste masking composition wherein the unpleasant taste masking composition comprises a medicament drug 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose in an amount of from about 0.001% to about 5.0%, by weight to nullify the bitter taste or unpleasant off-note of the medicament drug.

13. A confectionery composition which comprises a confectionery base and an effective amount of an unpleasant taste masking composition wherein the unpleasant taste masking composition comprises a medicament drug having a bitter gtaste or unpleasant off-note and a chlorodeoxysugar derivative selected from the group consisting of chlorodeoxysucrose derivatives and chlorodeoxygalactosucrose derivatives and mixtures thereof in an amount from about 0.001% to about 5.0%, by weight to nullify the taste or unpleasant off-note of the medicament drug.

14. The confectionery composition of claim 3, wherein the chlorodeoxysugar derivative is 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose.

15. The confectionery composition of claim 13, wherein the medicament drug having a bitter taste or unpleasant off-note is selected from the medicament drugs consisting of analgesics, antiasmatics, antitussives, antihistamines, antinauseants, decongestants, alkaloids, laxatives, anticholesterolemic and antilipid agents, appetite suppressants, central nervous system stimulants, expectorants, anti-inflammatory agents, nutritional supplements and mixtures thereof.

16. The confectionery composition of claim 13, wherein the chlorodeoxysugar derivative is present in an amount from about 0.02% to about 1.0%, by weight of the composition.

17. The confectionery composition of claim 16, wherein the chlorodeoxysugar derivative is present in an amount from about 0.05% to about 0.5%, by weight of the composition.

18. A confectionery composition which comprises a confectionery base and an effective amount of an unpleasant taste masking composition wherein the unpleasant taste masking composition comprises a medicament drug and 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose in an amount of from about 0.001% to about 5%, by weight to nullify the bitter taste or unpleasant off-note of the medicament drug.

19. A pharmaceutical ingestible composition which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of an unpleasant taste masking composition wherein the unpleasant taste masking composition comprises a medicament drug having a bitter taste or unpleasant off-note and a chlorodeoxysugar derivative selected from the group consisting of chlorodeoxysucrose derivatives and chlorodeoxygalactosucrose derivatives and mixtures thereof in an amount of from about 0.001% to about 5.0%, by weight to nullify the taste or off-note of the medicament drug.

20. A method for preparing an unplesant taste masking composition comprising a medicament drug having a bitter taste or unpleasant off-note which comprises: admixing the medicament drug having a bitter taste or unpleasant off-note and a chlorodeoxysugar derivative selected from the group consisting of chlorodeoxysucrose derivaties and chlorodeoxygalactosucrose derivatives and mixtures thereof in an amount of from about 0.001% to about 5.0%, by weight to nullify the taste or off-note of the medicament drug.

21. The method of claim 20, wherein the medicinal agent having a bitter taste or unpleasant off-note is present in an amount from about 0.0001% to about 5.0%, by weight of the composition.

22. The method of claim 21, wherein the medicinal agent having a bitter taste or unpleasant off-note is present in an amount from about 1.0% to about 3.0% and the chlorodeoxysugar derivative is present in an amount from about 0.02% to about 1.0%, by weight of the composition.

23. The method of claim 22, wherein the medicinal agent having a bitter taste or unpleasant off-note is present in an amount from about 1.2% to about 2.5% and the chlorodeoxysugar derivative is present in an amount from about 0.05% to about 0.5%, by weight of the composition.

24. The method of claim 22, wherein the chlorodeoxysugar derivative is 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose.

25. The method of claim 20, wherein the medicament drug having a bitter taste or unpleasant off-note is selected from the group of medicament drugs consisting of analgesics, antiasmatics, antitussives, antihistamines, antinauseants, decongestants, alkaloids, laxatives, anticholesterolemic and antilipid agents, appetite suppressants, central nervous system stimulants, expectorants, anti-inflammatory agents, nutritional supplements and mixtures thereof.

26. A method for sweetening ingestible compositions which comprises adding to the ingestible composition an effective amount of an unpleasant taste masking composition wherein the unpleasant taste masking composition comprises a medicament drug having a bitter taste or unpleasant off-note and a chlorodeoxysugar derivative selected from the group consisting of chlorodeoxysucrose derivatives and chlorodeoxygalactosucrose derivatives and mixtures thereof in an amount of from about 0.001% to about 5.0%, by weight to nullify the bitter taste or off-note of the medicament drug.

27. The method of claim 26, wherein the medicament drug having a bitter taste or unpleasant off-note is present in an amount from about 0.0001% to about 5.0% by weight of the composition.

28. The method of claim 27, wherein the medicament drug having a bitter taste or unpleasant off-note is present in an amount from about 1.0% to about 3.0% and the chlorodeoxysugar derivative is present in an amount from about 0.02% to about 1.0%, by weight of the composition.

29. The method of claim 28, wherein the medicament drug having a bitter aftertaste or unpleasant off-note is present in an amount from about 1.2% to about 2.5% and the chlorodeoxysugar derivative is present in an amount from about 0.05% to about 0.5%, by weight of the composition.

30. The method of claim 26, wherein the chlorodeoxysugar derivative is 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose.

31. The method of claim 26, wherein the medicament drug having a bitter taste or unpleasant off-note is selected from the group of medicament drugs consisting of analgesics antiasmatics, antitussives, antihistamines, antinauseants, decongestants, alkaloids, laxatives, anticholesterolemic and antilipid agents, appetite suppressants, central nervous system stimulants, expectorants, anti-inflammatory agents, nutritional supplements and mixtures thereof.

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[54] **PHARMACEUTICAL CHEWING GUM CONTAINING ACETYLSALICYLIC ACID**

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[52] **U.S. Cl.** **424/441**; 424/439; 424/440

[58] **Field of Search** 424/441, 440, 424/439

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[57] **ABSTRACT**

The invention relates to stable, pharmaceutically usable chewing gum formulations which contain acetylsalicylic acid (ASA) as the active compound, and to a process for their preparation.

5 Claims, No Drawings

PHARMACEUTICAL CHEWING GUM CONTAINING ACETYLSALICYLIC ACID

This application is a continuation of application Ser. No. 824,425, filed Jan. 23, 1992, now abandoned.

The invention relates to stable, pharmaceutically usable chewing gum formulations which contain acetylsalicylic acid (ASA) as the active compound, and to a process for their preparation.

Acetylsalicylic acid is a medicament which has been known for a long time and has antipyretic, anti-inflammatory and analgesic properties. Acetylsalicylic acid is employed for relatively long periods of time and in high doses for the treatment of rheumatic diseases. Acetylsalicylic acid has an inhibiting action on platelet aggregation, the acetylation of platelet cyclooxygenase presumably playing an important role. This property of the substance is utilised in its use for the prophylaxis and treatment of thromboses and in the field of other cardiovascular diseases. Relatively low doses are effective in this indication.

Acetylsalicylic acid is absorbed relatively slowly. On oral administration, the blood level maximum is reached only after about 2 hours. The substance undergoes a metabolic change after this administration, in the course of which acetic acid is split off. The first step of this reaction is effected by the esterases of the mucosa, and the subsequent reaction by the esterases in the liver, plasma and erythrocytes. Because of the associated high rate of metabolisation, the slow absorption is particularly undesirable in the indication of platelet aggregation inhibition, since the unchanged acetylsalicylic acid molecule is the active form here.

Like other organic acids, acetylsalicylic acid has a locally irritating and tissue-damaging action. As a result of damage to the gastric mucous membrane, micro-haemorrhages occur not infrequently when this compound is used. Dangerous haemorrhages may occur if ulcers are present in the gastrointestinal region. The risk of damage to the gastric mucous membrane increases in this context as the dose administered increases.

For the abovementioned reasons, it is appropriate to seek pharmaceutical presentation forms for acetylsalicylic acid which on the one hand ensure rapid absorption and on the other hand have good gastric tolerance.

One possibility of solving the problems mentioned is to use effervescent formulations containing acetylsalicylic acid. However, these have the following disadvantages:

- A glass of clean water and at least 2 to 3 minutes' time are needed to take them. They are therefore not suitable, for example, for travelling.
- They usually have a high sodium content.
- Their preparation and packaging in moisture-proof packing agents must be carried out under a particularly low atmospheric humidity, and are therefore involved and expensive.
- Effervescent formulations are high-cost products.

Chewable compositions (chewing gum, bubble gum, stick gum) were already described in the last century, and chewing gums and chewable tablets with a medicinal use have also been known for a very long time. The first chewing gum formulation containing acetylsalicylic acid was brought onto the market in the USA in 1924.

Chewing gum formulations which contain acetylsalicylic acid are also mentioned in the literature. For example, U.S. Pat. No. 2,465,233 describes a chewing gum for the treatment of kinetoses which contains a combination of scopolamine hydrobromide and acetylsalicylic acid. EP 0,151,344 describes a chewing gum formulation which is suitable for the preparation of chewing gum tablets and can contain pharmaceutical active compounds, ASA being mentioned. EP 0,253,040 describes a process for the preparation of a chewing gum sweet, medicaments of the acetylsalicylic acid type being described as possible components.

All the examples mentioned have the common serious disadvantage that when the formulation is chewed in the mouth, a solution of low pH is formed. This solution leads to irritation of the oral mucous membrane and damage to the tooth enamel, and the last point in particular is currently regarded very critically from the point of view of caries prevention. FR 87/02,939 offers a solution to this problem, in which the lysine salt of acetylsalicylic acid is employed here as the active compound in a buccal medicament form. However, no medicament forms which have an adequate chemical stability can be prepared in the manner described in that publication. The resistance of acetylsalicylic acid to hydrolysis decreases as the pH increases. The stability optimum is in the pH range of 2 to 3 (compare DAB 9, page 769, commentary). It is also expressly pointed out there that ASA is incompatible with alkaline substances. This means that all salts, including the lysine salt, have a lower stability than the free acid. Since the preparation of stable formulations of the free acid is already associated with major difficulties, even less success is to be expected when salts of acetylsalicylic acid are used.

It has now been found, against expectations, that with the composition according to the invention and the use of a specific preparation process it is possible to prepare stable, pharmaceutically usable ASA-containing chewing gum formulations which eliminate all the abovementioned disadvantages and are suitable for administration of all the customary doses of ASA. Astonishingly, it has been possible to combine the advantages of the buccal medicament forms already known, that is to say the good mucous membrane and mucosa tolerance of the chewing formulation containing ASA on the one hand and the good stability of the medicament forms containing the free acid on the other hand by the formulation according to the invention, without the particular disadvantages having to be the price.

The invention relates to a stable chewing gum formulation which is tolerated by the mucous membrane and contains acetylsalicylic acid as one component and a basic substance suitable for salt formation as the second component in a spatially separated form. During the chewing operation, the two components are dissolved out of the matrix and react immediately in the form of an acid-base reaction to give the particular readily soluble salt of acetylsalicylic acid. During storage of the formulation, the ASA is present as the free acid and therefore has a correspondingly high chemical stability, and the salt of ASA or a solution of this salt, which has a considerably improved mucous membrane tolerance compared with the free acid and attacks the tooth enamel less, is formed during the chewing operation.

The chewing gum formulation according to the invention preferably has the following composition:

Acetylsalicylic acid	2–30 parts by weight corresponding to 30–1500 mg
Basic buffer substances	corresponding to 0.1–17 meq* buffer capacity
Chewing gum base	15–50 parts by weight
Plasticiser	0–30 parts by weight
Sugar and/or sugar substitutes	0–55 parts by weight

-continued

Sweetener	0–2 parts by weight
Aroma substances	0–5 parts by weight
Fillers	0–30 parts by weight
if appropriate other components such as waxes, emulsifiers; stabilisers	0–20 parts by weight
if appropriate water-soluble polymer	0–30 parts by weight

*corresponding to USP XXII

Chewing gum bases as a rule consist of two main components which are needed to achieve the desired chewing gum properties. An elastomer component A represents the water-insoluble content which forms the volume, and a resinous, similarly water-insoluble component B is responsible for the constant chewability of the material. Both the elastomer component A and the resinous addition B can be of natural or synthetic origin. A combination of naturally occurring and synthetic material is also possible.

Possible elastomer components A are all the elastomers which are known to the expert and are physiologically tolerated. These can be, for example: natural rubber, such as chicle, polyvinyl acetates, isobutylene-isoprene copolymers, styrene-butadiene copolymers, polyiso-butylene, guttapercha, crown rubber, polyisoprene, polyethylene, naturally occurring polyterpenes and mixtures of these.

The resin components B usually used are, for example, Arkon P, polyvinyl esters of suitable molecular weight (for example polyvinyl acetate of molecular weight 20,000), copolymers of vinyl esters and vinyl ethers, polyethylene-vinyl acetate copolymers and natural resins, such as, for example, dammar and guaiacum.

Commercially available chewing gum bases can also be used according to the present invention as matrices for the chewing gum composition. Basic buffer components which can be employed are alkaline earth metal carbonates, preferably calcium carbonate; however, it is also possible to use calcium hydroxide, magnesium hydroxide, light magnesium carbonate, heavy magnesium carbonate or magnesium oxide. Other possible basic components are, for example, tris-(hydroxymethyl)-aminomethane, alkali metal phosphates or alkaline earth metal phosphates and basic amino acids. The amount of basic component is chosen according to the invention so that, together with the amount of acetylsalicylic acid employed, a buffer capacity of between 5 and 15 mEq results.

If appropriate, other constituents known to the expert for plasticising and texturising, for example fats and waxes, emulsifying, for example lecithin, filling, for example talc, aromatising and/or for establishing other required properties can be incorporated into the chewing gum base. The chewing gums can be sugar-free or can contain sugar. Compounds which are suitable for sweetening are sugars and sugar substitutes, such as mono- and disaccharides, hydrolysates of high molecular weight carbohydrates and sugar-alcohols. All or some of the amount of these substances can also be replaced by sweeteners, such as, for example, saccharin, cyclamate or aspartame.

The chewing gum base consisting of components A and B, including the additives mentioned, is called the chewing gum matrix below.

The constituents of a chewing gum formulation which are usually automatically necessary are the water-insoluble inert chewing gum base and the water-soluble content which is gradually dissolved out of the chewing gum matrix by the saliva during chewing. The formation of a (salt) solution of ASA from the formulation according to the invention in the saliva in the mouth is desirable for the following reasons:

in this way acetylsalicylic acid enters the stomach only in dissolved form, so that the formation of areas of high active compound concentrations in the stomach is avoided. This achieves an optimum gastric tolerance in the region of that of an effervescent tablet.

Significant amounts of the substance can already be absorbed from the saliva solution via the oral mucous membrane regardless of the residence time in the mouth. Acetylsalicylic acid in this way passes rapidly and in non-metabolised form into the circulation and can display its action there rapidly and effectively.

The abovementioned problem that the active compound solution formed in the mouth can cause damage to the oral mucous membrane and in particular the teeth is solved according to the invention by addition of a basic component which converts the chewing gum into a buffered formulation. Scanning electron microscopy examinations of extracted human teeth show that the damage to tooth enamel caused by solutions of acetylsalicylic acid can be reduced drastically and brought within the range of a placebo solution by suitable buffering. The risk described for some chewing tablets known to date that, for example, pieces of tablet which have remained in the cheek pouch overnight can cause severe inflammations of the oral mucous membrane also does not exist with the new chewing gum formulation, since acetylsalicylic acid emerges from the chewing gum matrix only in dissolved and therefore readily mobile form and at the same time is buffered. Local toxic concentrations are therefore not to be feared with the form according to the invention.

To prevent the known hydrolytic decomposition of acetylsalicylic acid, and in particular of its salts, which is accelerated considerably by heat, moisture and alkaline substances, the following measures are used individually or in combination in the preparation, according to the invention, of the formulation:

1. the water content of the product is kept as low as possible,
2. the exposure to heat during the preparation is kept low and
3. the acetylsalicylic acid is separated spatially from the basic component.

Re 1.:

A chewing gum matrix having a water content of not more than 2%, preferably up to 1%, in particular up to 0.3% (per cent by weight) is used for the chewing gum formulation according to the invention. To achieve the desired low water content, in particular the chewing gum bases, the plasticisers and the sweeteners should be of low water content and only slightly hygroscopic.

Re 2.:

Temperatures of more than 90° C. are often used in the preparation of chewing gum. In contrast, a maximum temperature of 85° C. is not exceeded in the preparation according to the invention of the chewing gum described. The ideal process temperature for the preparation is 40° C. and the preferred temperature range according to the invention is between 20 and 85° C., in particular between 30 and 60° C.

Re 3.:

a) Direct contact between the active compound component ASA and the basic component in the formulation is prevented by the two components being incorporated independently of one another and individually into a relatively large amount of chewing gum matrix, so that most of the acid particles are embedded individually in the matrix and are separated from their adjacent basic particles by the chewing gum base or the other additives and vice versa. As a result of the water content of the matrix being low

according to the invention, solution processes and diffusion via the liquid phase are not to be expected.

b) If it is necessary, for example at high concentrations of acetylsalicylic acid and basic buffer substance, to realise a more complete spatial separation of the two components, a preferred embodiment is to additionally coat one of the two substances or even both substances with a protective separating layer. The separating layer consists, for example, of a water-soluble polymer film which is applied to the substance to be protected. Hydroxypropylmethylcellulose (HPMC) is particularly preferably used as the water-soluble polymer, but it is also possible to use other cellulose derivatives or water-soluble polymers, such as starch derivatives, polyacrylates, alginates and the like. The polymer is used in an amount by weight of 1 to 100% of the core weight of the substance to be coated, such as ASA or base. The coating weight is preferably between 5 and 30% of the core weight, the amount to be particularly preferably applied depending on the particle size of the core particles.

The preferred process for application of the protective separating layer is spraying of the polymer from an aqueous solution onto the material to be coated.

The basic component is preferably coated or granulated with the water-soluble polymer, since this avoids the risk that the acetylsalicylic acid will be decomposed by hydrolysis during the coating process.

c) Another possibility of spatial separation of the two components comprises first incorporating the basic component into one half of the chewing gum base. ASA is then incorporated into the other half of the corresponding chewing gum base. Contact between the two compounds is largely avoided in this preparation process, since there is merely a reduced possibility of contact during subsequent common mixing and shaping of the two "prebatches". Most of the powder particles in these mixtures are also embedded in the chewing composition in isolated form. This process, which is comparable to a), thus represents a further improvement on the basis of the modified mixing procedure.

d) A significantly improved spatial separation can also be achieved by bringing the "prebatches" described under c) together in a final shaping operation without the compositions being mixed directly during this operation. Processes which are suitable for this are, inter alia, coextrusion via multilayer dies (adapter and in particular die coextrusion to give multilayer films/sheets) and, for example, calendering processes for the production of multilayer systems. All the apparatuses suitable in the rubber and foodstuffs industry can be used for this purpose.

The particular advantage of such a preparation process lies in the fact that the base compositions described under a), one of which contains the basic component and the other the ASA, come into contact merely via the "interfaces" of the coextrudates or films. This process is therefore particularly suitable for formulations with a high active compound concentration, since mixing of the base compositions during preparation is excluded. Each individual particle is thus present in the matrix in isolated form, which ensures a high storage stability.

e) Another possibility for spatial separation of the two individual components comprises modification of the operation, described under c), of separate mixing of the two components into a base chewing composition such that one component is first incorporated into the chewing gum base in the customary manner. The second component is then incorporated into a physiologically acceptable polymer composition which is only partly compatible with the chewing gum base. Subsequent joint compounding of the two base compositions in customary mixing units, such as, for example, kneaders, mills or extruders, leads to generally known morphological structures on the basis of the partial compatibilities existing between the two polymer systems. In these structures, for example, one component is present as a dispersion in the other. Such a structure is in principle related to that described under d), since here also contact is possible only via "interfaces" (matrix and disperse components). However, these structures offer the advantage that there is already a tight spatial closeness between the two components here over the entire homogeneously mixed blend, without contact between the two components being possible. The desired salt formation during a subsequent chewing operation can thus take place much more rapidly.

The chewing gum compositions are obtained by bringing the chewing gum base, if appropriate the other additives, the acetylsalicylic acid and the (optionally coated) basic component into contact in a mixing unit. Solid particles having a particle size of less than 50 μm are particularly preferred. Although higher particle sizes can be incorporated without problems, a modified chewing sensation is to be expected.

The chewing gum compositions according to the invention can be prepared by various processes. The process can be carried out discontinuously or continuously. Customary processes are, for example, preparation on mixing mills, kneaders and extruders. All the customary apparatuses and methods for the preparation of chewing gum are generally suitable for the preparation of the chewing gum compositions according to the invention. Processing of the chewing gum compositions to strips, tablets or balls and packaging thereof are also carried out by customary methods and can be undertaken on any known machine suitable for shaping and packaging chewing gum.

The chewing gum compositions according to the invention are preferably prepared by rolling the chewing gum base on a heatable roll at a roll speed of about 10–40 revolutions per minute in a temperature range from 20 to 85° C. for some minutes, subsequently adding acetylsalicylic acid, flavouring substances, plasticisers and if appropriate other auxiliaries and if appropriate then adding the basic buffer substance directly or incorporating the basic buffer substance in a portion of the chewing gum base on a correspondingly heated roll in a separate process step, the compounding time in each case being between 3 and 15 minutes, subsequently removing the chewing gum composition from the roll and, after cooling to room temperature, further processing the composition to finished chewing gum formulations in the customary manner.

At no point in time should the roll temperature exceed 85° C., preferably 60° C. If necessary, the roll temperature is reduced by cooling if heat of friction which is too high occurs.

The chewing gum formulations according to the invention prepared in this way offer the advantage of rapid absorption of the acetylsalicylic acid which is already present in dissolved form in the mouth, the advantage of a good tolerance in the mouth and in the stomach due to salt formation and buffering of the resulting solution during the chewing operation, the advantage of a high bioavailability due to the low metabolisation on buccal absorption, and the advantage of a high storage stability, since the acetylsalicylic acid is present as the free acid during storage. The disadvantages of the ASA-containing medicament forms known to date, each of which offer only one or not more than two of the advantages mentioned, are avoided by the formulation according to the invention.

EMBODIMENT EXAMPLES

Example 1

(variant 3a)

Cafosa Gum Base TAB-3-T	32	g
Sugar	44	g
Cafosa Plasticiser 1001-01	3	g
Optamint peppermint (H&R)	4.2	g
Citric acid	0.8	g
ASA	10	g
Calcium carbonate	6	g

32 g of a chewing gum base (Cafosa Gum Base TAB-3-T) are introduced onto a roll heated at 50° C. and rolled for 3 minutes. 44 g of sugar are then added. After about 3 minutes, a homogeneous mass is obtained, into which the other components are incorporated individually in succession. The peppermint flavouring substance (4.2 g) and the citric acid (0.8 g) are first added. 3 g of Cafosa Plasticiser 1001-01, 6 g of basic buffer substance (calcium carbonate) and 10 g of ASA are then incorporated. After a total milling time of 10.5 minutes, the chewing gum composition is removed from the roll. After cooling to room temperature, the finished material can be further processed to any desired shape.

Example 2

(variant 3b)

Cafosa Gum Base Dorada Plus-T	32	g
Sorbitol powder	22.8	g
Xylitol powder	5	g
Optamint peppermint (H&R)	4.5	g
Cafosa Plasticiser 1001-01	2	g
Aspartame	0.5	g
ASA	20	g
Calcium carbonate	12	g
HPMC	1.2	g

32 g of Gum Base Dorada Plus-T are introduced onto a roll heated to 60° C. and rolled for 3 minutes. 22.8 g of sorbitol powder and 5 g of xylitol powder are then added to this chewing gum matrix. After a further rolling time of 3 minutes, 4.5 g of Optamint peppermint flavouring substance, 0.5 g of aspartame and 2 g of Cafosa Plasticiser are added. Finally, 20 g of ASA and 13.2 g of calcium carbonate/HPMC are incorporated. For this, 12 g of calcium carbonate are treated by spraying on a separating layer of 1.2 g of HPMC (hydroxypropyl-methylcellulose) in a preceding operation for the purpose of complete spatial separation from the acetylsalicylic acid.

Example 3

Cafosa Gum Base TAB-3-T	30	g
Sorbitol powder	19.5	g
Na cyclamate/ Saccharin Na	0.5	g
Ascorbic acid	1	g
ASA	30	g
Calcium carbonate	18	g
HPMC	1	g

This chewing gum composition is prepared analogously to Example 2.

Example 4

(variant 3c)

Cafosa Gum Base Dorada Plus-T	30	g
Sugar	15	g
Sorbitol powder	29	g
Ascorbic acid	1	g
ASA	15	g
Calcium carbonate	10	g

To prepare this chewing gum composition, 30 g of Cafosa Gum Base Dorada Plus-T are rolled on a laboratory roll at 45° C. for 3 minutes. 15 g of sugar, 29 g of sorbitol powder and 1 g of ascorbic acid are then added. The mixture is rolled for a further 4 minutes until a homogeneous material is obtained. The chewing gum composition is then divided into two halves (prebatches 1 and 2). 15 g of ASA are incorporated into one half (prebatch 1) over a milling time of 2.5 minutes, and 10 g of calcium carbonate, as the basic buffer substance, are incorporated into the other half (prebatch 2). As a result, most of the ASA and base particles are present in these mixtures embedded in the chewing gum composition in isolated form. The preparation of prebatches 1 and 2 is followed by a very short joint mixing operation and subsequent shaping.

Example 5

(variant 3d)

Cafosa Gum Base TAB-3-T	28	g
Sorbitol powder	39.5	g
Na cyclamate	0.5	g
ASA	20	g
Calcium carbonate	12	g

Two prebatches are first prepared according to Example 4, one of which contains the total amount of ASA corresponding to the recipe and the other prebatch containing the total amount of calcium carbonate corresponding to the recipe. The two prebatches are passed to a unit for preparation of multilayer systems and are brought together such that there is no direct mixing of the compositions here. For this purpose, the prebatches are fed to two separate feeding devices of a coextruder and are then coextruded to strands at a die temperature of not more than 85° C.

Example 6

Chewing gum base 1	13	g
Chewing gum base 2	14	g
Cafosa Plasticiser 1001-01	3	g
Sugar	15	g
Sorbitol powder	29	g
Ascorbic acid	1	g
ASA	15	g
Calcium carbonate	10	g

To prepare this chewing gum composition, two different chewing gum bases which are only partly compatible with one another are used. All the polymers which are suitable for preparation of chewing gum bases (compare page 6) and have a mutual partial compatibility can in principle be used here.

To prepare this chewing gum composition according to the invention, 13 g of a chewing gum base 1 which contains natural rubber are rolled on a laboratory roll at 85° C. for 3 minutes. 7.5 g of sugar, 14.5 g of sorbitol powder, 1.5 g of

Cafosa Plasticiser, 15 g of ASA and 1 g of ascorbic acid are then added. The mixture is rolled for a further 4 minutes until a homogeneous material is obtained (prebatch 1). Another prebatch consisting of 14 g of the chewing gum base 2 containing styrobutadiene copolymer, 7.5 g of sugar, 14.5 g of sorbitol powder, 1.5 g of Cafosa Plasticiser and 10 g of calcium carbonate is then prepared by the same procedure (prebatch 2). Final joint compounding of the two prebatches in a mixing kneader leads to generally known morphological structures, on the basis of the partial compatibility which exists between the two chewing gum bases, in which one chewing gum base is present as a dispersion in the other.

We claim:

1. An acetylsalicyclic acid-salt releasing chewing gum comprising acetylsalicylic acid, and a basic substance capable of reacting with said acetylsalicylic acid to form an acetylsalicylic acid salt, said gum containing not more than about 2% of water and said acetylsalicylic acid and said basic substance being bound in said chewing gum apart from each other sufficiently to prevent them from reacting with each other until said chewing gum is chewed, which gum when chewed in the presence of saliva brings said acetylsalicylic acid into contact with said basic substance so that they react to form said acetylsalicylic acid salt which is then rapidly released to the saliva, said basic substance being selected from the group consisting of an alkaline earth metal carbonate, calcium hydroxide, magnesium hydroxide, light magnesium carbonate, heavy magnesium carbonate or magnesium oxide, tris-(hydroxymethyl)-aminomethane, alkali metal phosphates or alkaline earth metal phosphates and basic amino acids, the amount of basic substance being such that together with the amount of acetylsalicylic acid employed there results a buffer capacity of between 5 and 15 mEg.

2. Chewing gum formulation according to claim 1, having the following composition:

Acetylsalicylic acid	2–30 parts by weight corresponding to 30–1500 mg
Basic buffer substances	corresponding to 0.1–17 meq buffer capacity
Chewing gum base	15–50 parts by weight
Plasticiser	0–30 parts by weight
Sugar and/or sugar substitutes	0–55 parts by weight
Sweetener	0–2 parts by weight
Aroma substances	0–5 parts by weight
Fillers	0–30 parts by weight
waxes, emulsifiers, stabilisers	0–20 parts by weight
water-soluble polymer	0–30 parts by weight.

3. Chewing gum formulation according to claim 1, per 100 parts by weight consisting essentially of

Acetylsalicylic acid	2–30 parts by weight corresponding to 30–1500 mg
Basic buffer substances	corresponding to 0.1–17 meq buffer capacity
Chewing gum base	15–50 parts by weight
Plasticiser	0–30 parts by weight
Sugar and/or sugar substitutes	0–55 parts by weight
Sweetener	0–2 parts by weight
Aroma substances	0–5 parts by weight
Fillers	0–30 parts by weight
Waxes, emulsifiers, stabilizers	0–20 parts by weight
Water-soluble polymer	0–30 parts by weight
Water	0–2 parts by weight.

4. Chewing gum formulation according to claim 1, characterized in that the spatial separation between the components acetylsalicylic acid and the basic buffer substance is ensured by one or more of the following measures:

a) the two components are incorporated independently of one another and individually into the chewing gum matrix,

b) one or both components are coated with a protective separating layer of a water-soluble polymer film,

c) the two components are in each case incorporated independently of one another into the chewing gum composition and these compositions are mixed just before shaping or coextruded via multiple dies, or

d) the two components are in each case incorporated independently of one another into different chewing gum bases or polymer compositions which are only partly compatible with one another, a two-phase system being formed during joint compounding and shaping of the two matrices.

5. Process for the preparation of chewing gum formulations according to claim 1, characterized in that the acetylsalicylic acid, the chewing gum base, and additives and the basic component, which is optionally coated and/or worked into a chewing gum base which is optionally partly compatible, are converted into application form continuously or discontinuously in a mixing unit at temperatures between 20 and 85° C.

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